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CARDIAC VALVE CALCIFICATIONS AND REGISTRATION OF THEIR MOVEMENTS

by

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According to WARTMAN and HILL (34), calcifications of the heart may be either metastatic or dystrophic. The former, which are rare, are associated with increased availability of calcium and usually occur in connection with calcifications in other organs, especially the lungs, stomach, kidneys, liver, and spleen. They are found in cases of destructive bone lesions, hyperparathyroidism, hypervitaminosis D, and kidney insufficiency; in the heart, this type of calcification is commonly encountered in the hyaline structures, *e. g.* the endocardium.

Dystrophic calcifications, which are much more common in the heart, may occur without change in the physiologic levels of any of the chemical constituents of the blood. They may also be situated in any part of a devitalized tissue which is large enough to prevent resorption. Dystrophic calcifications in the ostia occur particularly in the aortic and mitral orifices where they are situated in the valves, and annulus fibrosus. Calcifications are rare in the tricuspid and pulmonary ostia and only a very few cases have been described (7, 31, 27). These dystrophic calcifications occur after either an inflammatory or a degenerative atherosclerotic process. It appears from the literature that the words 'cusp' and 'valve' are often employed as if possessing the same meaning. The author in this

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paper uses the word 'cusp' to mean the individual cusp and confines the use of the word 'valve' or 'valves' to the collection of cusps which form an entity at one or more ostia.

In cases of inflammatory genesis the most common cause is rheumatic verrucous endocarditis. Subjects with healed bacterial endocarditis may, however, also have valve calcifications (28). The calcifications are generally localized to the cusps but may also spread to close-lying structures such as the annulus fibrosus, chordae tendinae, papillary muscles, and the endocardium. They occur both in young and aged subjects. EPSTEIN (6) has observed calcifications of the mitral valve in a 13-year-old patient. Calcifications due to a degenerative atherosclerotic process are particularly likely to be observed in the aged, often in connection with other atherosclerotic manifestations.

Certain authors (10, 31) consider that the genesis of calcifications in the aortic valve is always rheumatic although others (20, 24, 1, 15) have shown in autopsy material that the cause often is atherosclerosis. ASHWORTH found that the most common situation of atherosclerotic calcifications were the aortic cusps, followed by the sinuses of Valsalva, annulus fibrosus mitralis, annulus fibrosus aortae, septum intervalvulare, and the proximal part of the anterior mitral cusp.

Endocarditic valve calcifications because of their situation in the verrucae, at least in the earlier stages resemble a string of pearls. Atherosclerotic valve calcifications are more irregular whereas the calcification in the annulus fibrosus mitralis is often homogenous, U-, J-, or comma-shaped. In the later stages it may be difficult to distinguish roentgenologically between endocarditic and atherosclerotic calcifications, particularly when situated in the aortic ostium. In the mitral valve, atherosclerotic calcifications are rarely so dispersed as the endocarditic.

Heart valve calcification in relation to valvular heart disease. Subjects with endocarditic calcifications always have valvular heart disease. Atherosclerotic valve calcifications occur especially in the aorta in cases of stenosis and/or insufficiency, without any known rheumatic genesis (20, 7, 24, 1, 15). Even extensive calcifications however, may occur in the aortic valve without any demonstrable valvular heart disease. Valvular dysfunction with stenosis and insufficiency, due to atherosclerosis, has been described in a few cases of mitral disease (24, 1).

Most authors are of the opinion that calcification of the annulus fibrosus mitralis does not cause valvular dysfunction (31, 8 and others). SIMON and LIU, however, in an autopsy material, described the occurrence of insufficiency in the mitral valve in 9 out of 24 cases with calcifications of the annulus fibrosus mitralis and without changes in the cusps. In view of our present knowledge of the contracting mechanism of the mitral valve (16),

it is plausible that extensive calcification in the annulus fibrosus hinders muscular contraction of the ring and thus reduces the possibility of the cusps preventing regurgitation.

Frequency of calcifications in autopsy material. Calcifications are common in valvular heart diseases of inflammatory genesis. EPSTEIN (7) found valve calcifications in 64 out of 148 cases, *i. e.* 47 %; most of these calcifications (38 cases) were localized to the mitral valve, while 26 were found only in the aortic or in both the aortic and mitral valves. In addition to calcifications in the aortic and mitral valves 2 cases also had calcifications in the tricuspid valve. HOLZMANN (12) examined an autopsy material comprising 28 cases of aortic stenosis, 75 % of which were rheumatic. He found calcifications in 23, *i. e.* in approx. 80 % of the cases.

Calcifications of non-inflammatory genesis have been observed in varying frequencies, depending on the composition of the autopsy material (1, 7, 15). The frequency increases with age, and in a material of cases aged more than 50 years ASHWORTH found calcifications in the mitral ring and aortic ostium in 42 %. HULTGREN claims that practically all patients over 60 years have calcifications in the aortic ostium. Calcifications in the mitral ring, which as a rule have no inflammatory genesis, are also common and have been observed in about 5 to 10 % of cases in a non-selected autopsy material (21, 8, 29).

Roentgenologically demonstrable calcifications. In perusing the literature, I have not been able to find any significant figures indicating how often calcifications can be roentgenologically demonstrated. HOLZMANN (12) found calcifications in 3 out of 5 cases of aortic stenosis. In cases of inflammatory genesis, SOSMAN (31) believes it possible to demonstrate calcifications in 10 % of mitral and 90 % of aortic valvular disease, and adds that in a hospital containing 250 beds, hardly any week passes without his finding a case with a calcification of the heart. In about six months, we have encountered a total of about 30 cases of aortic and mitral valve calcifications in some 500 roentgen examinations of the heart in our department. Most of these 500 patients had no valvular or other heart disease. It is therefore evident that calcifications in the ostia of the heart are common and often possible to demonstrate roentgenologically. Their demonstration may be of value for the diagnosis of valvular diseases and the selection of cases for operation, and to a certain extent may be of prognostic and etiologic importance.

In certain cases it is difficult or even impossible clinically to arrive at a diagnosis of aortic (12) or mitral (30) valvular disease. Furthermore, the characteristic roentgenologically demonstrable change in the shape of the heart may be absent. The demonstration of valve calcifications may

therefore occasionally be decisive in the diagnosis, particularly in multivalvular changes. Since the introduction of the surgical treatment of valvular disease, precise information with regard to their localization and nature has naturally become more important. CARLGREN and PETTERSSON reported that no improvement or even impairment followed operation for mitral stenosis in about 50 % of cases in which extensive mitral valve calcifications were present. WYNN found that 50 % of cases of mitral stenosis with large calcifications also had significant insufficiency, which means twice as often as in other cases without large calcifications. As, in addition to this, MCMILLAN has shown that cases with aortic stenosis and large calcifications could not be expected to improve after valvotomy, it is evident that the demonstration of calcifications is of importance when selecting cases suitable for operation.

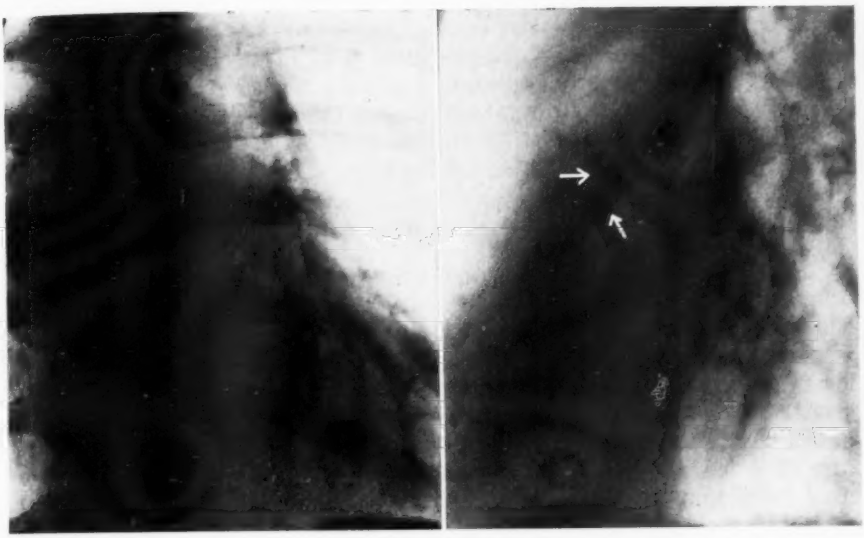
According to certain authors (8, 1), general atherosclerosis occurs more frequently in subjects with atherosclerotic calcifications of the valves and the demonstration of these may therefore be of prognostic importance.

Finally, the appearance of the calcifications is sometimes such as to give a hint about the etiology of the heart disease. Calcifications resembling a string of pearls in both aortic and mitral valves as well as large mitral valve calcifications are typical of endocarditis, while large calcifications in the aortic ostium may appear both after inflammatory and degenerative atherosclerotic processes (Fig. 1).

Calcifications may be demonstrated by fluoroscopy, conventional roentgenography, or tomography.

Fluoroscopy is valuable providing as it does the possibility of observing movement. The eyes of the examiner must naturally be well adapted, at least unless an image intensifier is employed. The possibilities of demonstrating calcifications increase considerably if the examination is performed with a short distance, small diaghragm, high voltage (about 110 kV), and high current (about 5 mA). When this technique is used the screening time must be short and small calcifications of low density may consequently be overlooked. As cinematography makes repeated studies of motions possible, a calcification may exceptionally be demonstrated only by means of this method. This has once happened to the present author. Thus, in one case I was able to see the calcification properly only after studying the motion picture several times. The most suitable positions for demonstrating both aortic and mitral valve calcifications are the right anterior and the true lateral projections.

Conventional roentgenography with only p. a. and true lateral views is an unsuitable method, especially if the calcification is small, or situated



a b

c

Fig. 1. Case 1.

Aortic stenosis with pearl-string-like calcifications in the aortic valve. Normal size and shape of the heart. The clinical diagnosis was somewhat uncertain until the calcifications were shown.

a) and b) P. a. and true lateral views. The calcifications can hardly be seen.

c) Oblique view. Calcifications clearly visible.

in the aortic ostium; this latter is usually obscured by the spine in the p. a. projection. Supplementary oblique films may increase the possibility of demonstrating valve calcifications, especially if the examination is performed as described by ODQVIST (21) among others, viz. at a short distance with the shortest possible exposure time and smallest diaphragm. If careful fluoroscopy has been performed the films merely confirm the previous findings; even if the correct technique is used, it may be impossible to obtain convincing representations of small calcifications.

Tomography may be of value owing to the possibility of blurring other calcifications, *e. g.* in the costal cartilages, lymph nodes, or lungs. The exposure time is relatively long in tomography. The shortest exposure time with the apparatus at our disposal is 1.7 sec, a period which covers at least one cardiac cycle. The motion of a small calcification will often render its demonstration impossible, especially as it may furthermore be out of the selected layer during certain phases of the cardiac cycle. In the case of a large calcification, on the other hand, the long exposure time may be advantageous; the calcification is reproduced in different positions which may give information as to both the minimum amplitude and the direction of movement, two factors which are important when localizing the calcification to a certain ostium.

The most reliable method for demonstrating calcifications, especially the smaller ones, appears therefore to be fluoroscopy, provided of course that the technique is suitable.

Localization of calcifications to a certain ostium. Calcifications in the tricuspid and pulmonary ostia are rare, and the problem therefore practically always lies in the differentiation between aortic and mitral valve calcifications. The position of the calcification affords a clue to its situation. According to SOSMAN (31), a calcification in the mitral valve is situated slightly lower than one in the aortic ostium. Furthermore, by using the left anterior projection recommended by him, the aortic ostium should be projected into the middle third and the mitral ostium into the posterior third of the heart. This method is generally applicable for extensive calcifications, but consideration must be given to changes in the relative size of the various heart chambers, which may alter the position of the ostia, as well as to the phase of the heart cycle in which the films are exposed. As the amplitude of the mitral valve is large, it seems that in a certain phase of the heart cycle (diastole, see below) in the left anterior position, the valve may be projected into the middle third of the heart. Small calcifications, particularly if situated in the anterior medial mitral cusp or in the posterior parts of the aortic ostium (Fig. 2), may be impossible to localize in this manner.

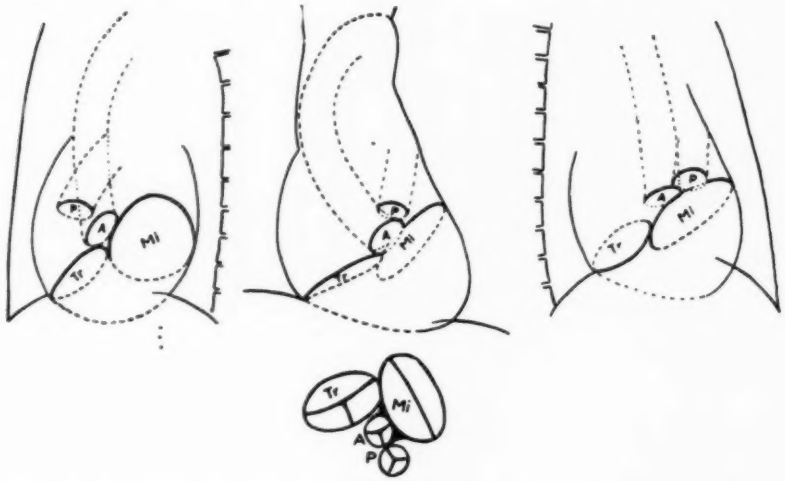


Fig. 2. Close proximity of the mitral and aortic valves. (After SCHINZ et coll.: Lehrbuch der Röntgendiagnostik, 1952, p. 2844).

The method mentioned may in certain cases therefore prove unreliable. As it is important to localize a calcification to a certain ostium, the question arises as to whether it is possible to localize calcifications by analysing their movements.

The movements of the valves have previously been studied in experimental investigations (5, 25, 26) and in human subjects with cardiac calcifications (32, 2, 3, 36, 37, 12, 33, 21, 22, 11, 14, 23, 9, 18, 17). DEAN has shown in perfused feline hearts that the mitral cusps move towards the atrium during ventricular systole and apically during the earlier part of diastole (isometric relaxation phase). RUSHMER et coll. (25) in 1955 arrived at similar results but in a later paper (26), in 1956, they altered their opinion and stated that the movements were incorrectly determined in their first paper (25) — the mitral cusps really move apically during ventricular systole and basally during diastole. Several authors (32, 2, 30, 21, 9) have studied mitral valve calcifications in man by fluoroscopy. All these authors, except FROMENT et coll., believe that the mitral cusps move apically during ventricular systole and basally during diastole. The last-mentioned authors as well as Mc KUSICK are of a contrary opinion, the latter having registered the movements by means of roentgenkymography. As regards the movements of the aortic valve, all authors except BLACKFORD et coll. are of the opinion that the valve moves apically in systole and basally in diastole.

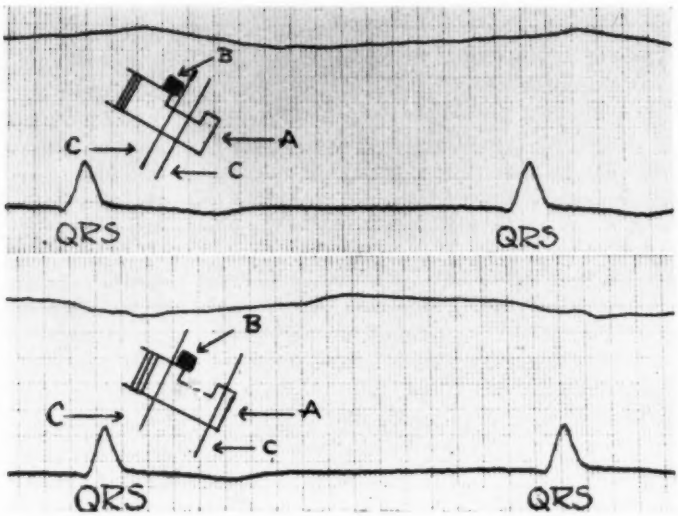


Fig. 3. Electrokymography. Aortic valve calcifications (Case 3). A: Phototube. B: Calcification. C: Diaphragms. Phototube placed over left ventricle. *Upper curve:* Diaphragms constricted and curve not influenced by calcification. A true ventricular pattern. *Bottom curve:* Diaphragms open but position otherwise maintained. Appearance of curve changed on account of increased density during systole, indicating an apical movement of calcification during this phase.

The movements of the calcified mitral ring have been studied by various methods, viz. cinematography (21, 22, 11), roentgenkymography (33, 18), and "Phasengezielten Herzaufnahmen" (14). It is generally considered that the ring moves apically during ventricular systole and basally during diastole. The amplitude of the aortic valve movement is given in the literature as 1 to 1.5 cm (12, 21), of the mitral valve as 0.5 cm (21) to 'large movements' (18), and of the mitral ring as 1 to 2 cm (33, 22, 11).

Own investigations

In the analysis of movement at least three factors may be expected to be of importance in the differential diagnosis, viz., its direction, its amplitude and its relation to the cardiac cycle.

Considering the position of the ostia, the direction of the movement should, from the theoretical point of view, give an idea as to the situation of calcifications. Both direction and amplitude may be determined approximately by fluoroscopy although the relation of the movement to the cardiac phase will not be evident, owing to the slow reaction of the eye.

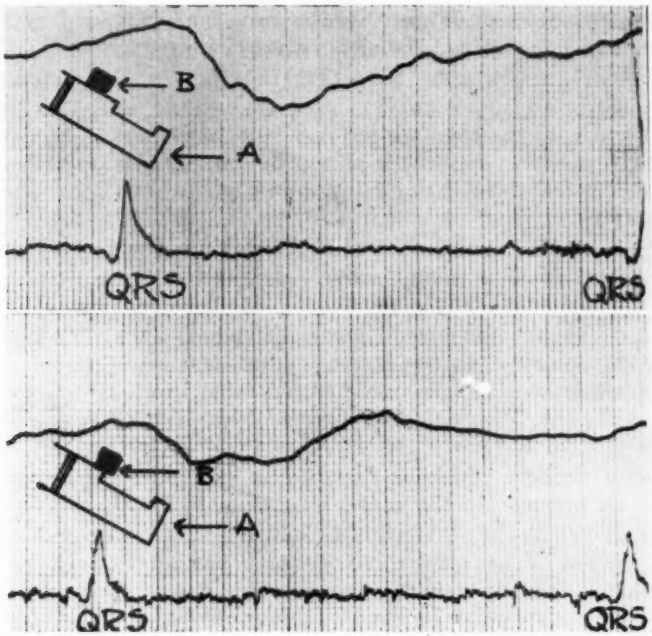


Fig. 4. Electrokymography. Mitral valve calcification (Case 5). *Upper curve*: Slit of phototube (A) placed slightly below calcification (B), which never appears in slit. Pattern of ventricular type. *Bottom curve:* Slit displaced slightly upwards, and calcification when moving apically appears in it. The curve changes because of increased density during the latter part of systole and earlier part of diastole. The calcification causes a change in the curve and thus moves apically during the end of systole or the beginning of diastole.

Determination of the direction can be effected objectively by double exposure — with or without tomography — which will reproduce the calcifications in different positions in the same film; in addition, a measure of the minimum amplitude is then obtained. In order to find out the true amplitude, the film must be obtained in a suitable projection and with the exposures in the most adequate phases of the cardiac cycle. (See Figs. 5 and 6.)

For the objective registration of the movement of the valve calcification in relation to the cardiac cycle, I have used both electrokymography and cinematography.

Electrokymography. The electrokymograph is coupled so that an increased density in the light-sensitive slit will be recorded as a rising part of the curve, and reduced density as a falling part. The movement of an

aortic valve calcification (Case 3) is shown in Fig. 3. The phototube was placed over the left ventricle in such a manner that the calcification, when moving apically, appeared in the upper part of the slit. The diaphragms are first constricted (upper curve) thus reducing the light-sensitive slit to such an extent that the calcification does not influence the curve, which is consequently a true ventricular one. The diaphragms are then opened (bottom curve) but the position is otherwise maintained. The appearance of the curve is changed on account of increased density during systole, indicating an apical movement of the calcification during this phase.

The movement of a mitral valve calcification (Case 5) is shown in Fig. 4. In the upper curve, the slit was placed slightly below the calcification which during its movements never appeared in the slit. The curve is of the ventricular type. In the bottom curve, the slit had been displaced slightly upwards so that the calcification when moving apically partly appeared in the slit. The curve has changed owing to an increase in density during late systole and early diastole. From the theoretical point of view, the increased density could be ascribed to the calcification, the aortic base, or to an atrium. As the aortic base (Fig. 5) moves upwards during this period, however, the curve cannot be influenced by the aorta. Furthermore, the curves of the electrokymographic densigram, as regards both aorta and atria, fall during this phase, and therefore it seems clear that the change in the curve must be due to the calcification. The calcification thus moves apically at the end of systole or at the beginning of diastole.

Cinematography for the study of the movements of the cusps in man has to my knowledge not been used before.

Seven valve calcifications in six patients have been examined and are briefly reported below.

Case reports

Case 1. Male, aged 34 years. Clinical diagnosis: Aortic stenosis. No known rheumatic infection. Systolic murmur present at the age of 12. Active sportsman, fulfilled military training, previously healthy. During the previous 4 to 5 years, he became easily tired with slight fainting attacks following exertion. There was no evidence of incompensation. A rough, sawing systolic murmur was heard over the entire heart, maximum in the right I 2, confirmed by phonocardiography. B. P. 105/75 in the horizontal position and 105/90 standing. ECG: Sinus rhythm and changes as in left ventricular strain. Low physical working capacity and delayed restitution following work. Clinical diagnosis considered somewhat uncertain.

At *roentgen examination* pearl-string-like calcifications in the aortic cusps were demonstrated. The size and shape of the heart were within normal limits. The diagnosis was later further confirmed, *i. e.* at *electrokymography*, when changes typical of aortic stenosis were found.

Case 2. Male, aged 26 years. Clinical diagnosis: Aortic stenosis. No known rheumatic infection. Consulted physician for insurance examination. Had a systolic murmur when seven years old and for this reason was exempted from gymnastics at school, but played football, went skiing, etc. without any reduced capacity. Military service as fatigue-duty man. Examination revealed no signs of incompensation. A systolic murmur was heard, maximum in the right I 3 to I 4 and confirmed by phonocardiography. B. P. 110/85. ECG: Normal with sinus rhythm. Physical working capacity slightly reduced.

Valvular heart disease was not suspected until pearl-string-like calcifications were demonstrated in the aortic valve at the *roentgen examination*. The heart was normal in size and shape. The diagnosis was later further confirmed, *i. e.* at *electrokymography*, when changes typical of aortic stenosis were found.

Case 3. Male, aged 62 years. Clinical diagnosis: Aortic stenosis and insufficiency. Acute rheumatoid arthritis at about 40 years of age. Heart trouble since about the age of 50 with dyspnoea, attacks of irregular cardiac activity, and pain in the left chest. Slight lip cyanosis but not other signs of incompensation noted. Heart: Systolic and diastolic murmur, maximum over the aorta. Second sound missing over the aorta. B. P: 190/90. ECG: Sinus rhythm. Left ventricular strain.

Roentgen examination of heart: Volume 1,100 cc corresponding to 650 cc/m² body surface. Left ventricle enlarged compared with other heart chambers. Large irregular calcifications in aortic valve. No pulmonary congestion.

Case 4. Male, aged 64 years. Clinical diagnosis: Mitral valve insufficiency and slight stenosis. No known rheumatic infection. Syphilis at the age of 20. Recent slight dyspnoea. In spring 1955, emboli in both legs. Apart from slight lip cyanosis, no signs of incompensation noted. Heart: Long systolic and short diastolic murmur with maximum at apex. B. P: 145/85. ECG: perpetual arrhythmia.

Roentgen examination of heart: Volume 1,700 cc corresponding to 800 cc/m² body surface. Enlargement especially of left atrium but also of left and right ventricles. Rather large, irregular calcifications in mitral cusps. No obvious pulmonary congestion.

Case 5. Male, aged 38 years. Clinical diagnosis: Mitral valve stenosis. No known rheumatic infection. Diagnosis of mitral stenosis made in 1948, when treated in a hospital for pneumonia. In 1954, cerebral emboli. Apart from lip cyanosis, no signs of incompensation noted. Heart: Diastolic murmur, sometimes presystolic, over apex. B. P: 120/95. ECG: perpetual arrhythmia.

Roentgen examination of heart: Volume 1,200 cc corresponding to 700 cc/m² body surface. Enlargement especially of left atrium but also of right ventricle. Calcifications in mitral cusps resembling string of pearls and slightly less regular calcifications in chordae tendinae.

Case 6. Male, aged 47 years. Clinical diagnosis: Mitral valve stenosis and insufficiency. No known rheumatic infection and no heart trouble up to the age of 38, when he started to get attacks of dyspnoea and pulmonary oedema. At the age of 43 (in 1951), valvotomy was performed for mitral valve stenosis when extensive calcifications in the mitral ostium and chordae tendinae were found. The surgeon felt a diffuse regurgitation flow which increased after valvotomy; patient improved considerably following operation. Present examination: No signs of incompensation. Heart: systolic and diastolic murmur over apex. B. P: 115/90. ECG: Sinus rhythm with delayed conduction and intraventricular block corresponding to right ventricle.

Roentgen examination of heart: Volume 910 cc corresponding to 470 cc/m² body surface. Enlargement of right ventricle and especially of left atrium. There were large irregular calcifications in the mitral valve and reaching into the chordae tendinae. Small calcifications were seen also in the aortic valve.

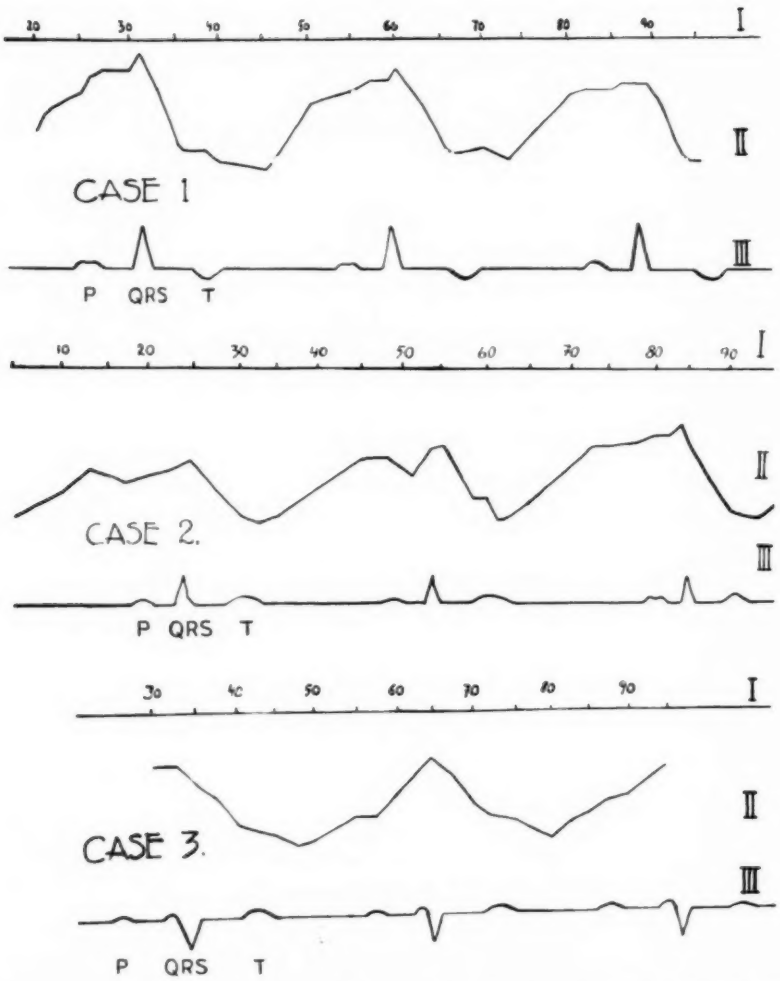


Fig. 5. Graphic reproduction of movements of aortic valve calcifications. Falling parts of curve II means a movement towards the apex while rising parts represent a movement towards the aorta. Synchronously, ECG, curve III, was taken and each exposure (40 frames/sec) registered in I. Aortic valve calcifications move apically rather rapidly during a phase corresponding to the isometric contraction period and the earlier part of ventricular systole; during diastole they move basally. The movements are continuous and their maximal amplitude is 0.5 to 0.8 cm.

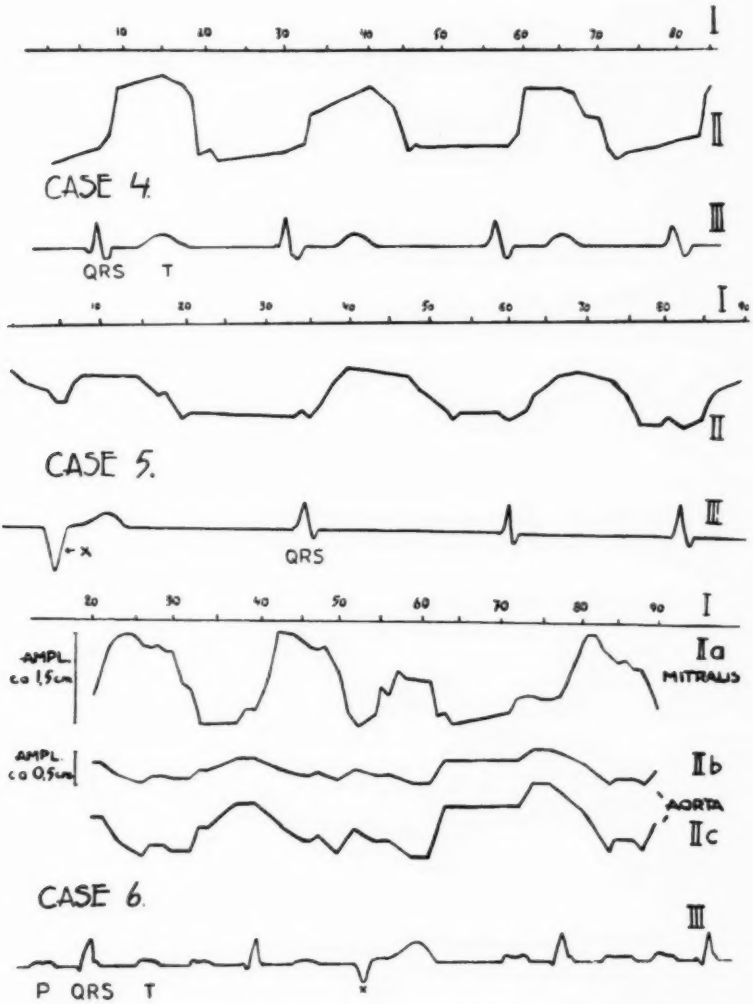


Fig. 6. Graphic reproduction of movements of mitral valve calcifications. Falling parts of the curves represent an apical movement, while rising parts mean one towards the left atrium. In Case 6, aortic valve calcifications are also present (II b and II c). Curves II-a and II-b are comparable in amplitude (II-c is a magnification from II-b). X = extrasystole. Calcifications of mitral valve move on the whole in opposite directions to those of the aortic valve. Movements are not continuous as in the aortic valve but there is an alternation between very rapid and practically no movements. Large maximum amplitude of about 1.5 to 1.9 cm.

All the patients with heart valve calcifications in the cases reported also had valvular heart disease. In 3 cases the calcification was situated only in the aortic valve, and in 2 only in the mitral valve. One patient had both aortic and mitral valve calcifications.

Cinematography was performed with the patients in a sitting position and with a camera mounted on a Philips image intensifier. Thirty five mm film was used and the speed was about 40 frames/sec. The position of the calcifications in each frame was copied, thus enabling a graphical registration of the movements. A synchronous ECG was taken, upon which each exposure was registered; the paper speed of the ECG was 10 cm/sec. In each patient the calcification was examined in at least two projections.

Results

Aortic valve calcifications (Fig. 5) move rather rapidly towards the apex during a phase corresponding to the isometric contraction period and the early part of the ventricular systole. During diastole, starting approximately when the aortic cusps close, the calcifications move towards the aorta. The most rapid movement during 0.025 sec (from one frame to the next) amounts to 0.2 to 0.3 cm. The amplitude of the entire movement varies between 0.5 and 0.8 cm. The *direction* of the main movement is almost vertical in the right anterior and true lateral views.

Mitral valve calcifications on the whole move in an opposite direction compared to those in the aortic valve in the different phases of the cardiac cycle. Thus, (Fig 6), during a phase approximately corresponding to the isometric contraction period and the early part of the mechanical ventricular systole, the calcifications quickly move towards the atrium and remain in a high position approximately until the rapid filling phase starts, when they quickly move towards the ventricle. They practically do not move during diastole. The maximum speed is high and in Case 4 amounted to about 1 cm during 0.025 sec. In Cases 5 and 6 the corresponding figures were 0.5 and 0.7 cm respectively (Fig. 7). The amplitude of the total movement is considerably larger than that of the aortic valve and amounts to 1.5 to 1.9 cm. The direction of movement in the right anterior and true lateral views is more horizontal than for the aortic valve. The mitral valve, in the cases examined, moves along a line which forms an angle of 45° to 60° with the horizontal plane.

The graphic curves for the movements of the calcified aortic and mitral valves do not in the main change when examined in different projections.

Discussion and Conclusions

Two objective methods, electrokymography and cinematography, have been used to register the calcified valve movements.

In cases with large calcifications it is possible to register the valve movements by means of electrokymography. This method however, only gives a rough idea of the movements and a detailed study is almost impossible as the examination is not a selective one. Small calcifications which are often the most difficult to localize, can hardly be examined by applying this method. They are either not sufficiently dense to alter the appearance of the curve or else so small that they lie inside the slit during the greater part of the cardiac cycle and for this reason do not alter the curve. The value of electrokymography in registering the movements of the valves is thus limited.

It is possible to record in detail the movements of even small calcifications by means of cinematography. Such an analysis is of importance from a practical as well as theoretical point of view. The movements of the aortic and mitral valve calcifications differ in direction, speed, and amplitude as well as in relation to the cardiac cycle. It is thus possible to localize a calcification to a certain ostium better than with any other method. In the cases of mitral valve calcifications with obvious signs of insufficiency (Case 6, and especially Case 4), the movements had a somewhat larger amplitude, started earlier, and were more rapid than in that case in which such signs were lacking (Case 5). As regards the cases with aortic valvular disease, a certain difference was found between Cases 1 and 2 with pure stenosis and Case 3 which had signs of insufficiency as well.

It therefore seems plausible that the valves in cases of aortic or mitral valve stenosis move slightly differently than in cases with additional insufficiency. Our case material is far too small, however, to be significant in this respect.

From a theoretical point of view it is of interest to study the movements of the valve calcifications in relation to the heart chambers and the aorta. In such an analysis it is necessary, however, to take into consideration the positional changes of the heart as well as the movements of the annulus fibrosus. The aortic cusps naturally move somewhat upwards into the aorta when the valve opens in systole; they are dominated, however, by the apical movement of the aortic ring and the relative movements of the cusps are therefore similar to those of the ring. Furthermore, when examining the movements of the aortic valve it is obvious that the valve moves slightly forwards as well as backwards, perhaps due to positional changes of the heart.

A change in the position of the heart cannot be decisive in calcifications of the mitral valve due to the speed and large amplitude of the

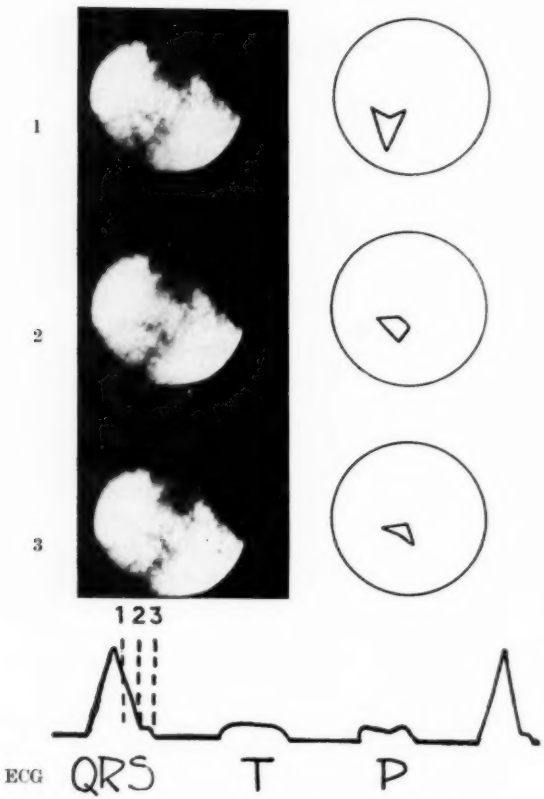


Fig. 7. Successive copies from a motion-picture of mitral valve calcifications (Case 6). True lateral, 0.025 sec between each exposure, which as is seen in ECG is made in early systole. Very rapid movement towards atrium.

valve movements. Both the speed and amplitude of movement of the mitral valve are considerably greater than those of the cardiac outline as registered by cinematography or electrokymography. It is not, however, possible from the present material to draw any definite conclusions as to the extent the movements of the mitral ring influence those of the cusps. As mentioned earlier the movements of the mitral ring have been studied by different methods, viz. cinematography, roentgenkymography, and with single exposures at certain phases of the cardiac cycle. All authors are of the opinion that the mitral ring moves apically during systole and towards the atrium during diastole. If this were so, the mitral ring would

move in an opposite direction to the mitral cusps, which means that the amplitude and speed of the cusp movement should be even greater than observed by me.

As far as I have been able to ascertain, ODQVIST (21, 22) and HOLMGREN (11) are the only authors who have used cinematography for this purpose. ODQVIST, however, has not correlated the movement of the calcifications to the cardiac cycle in an objective way but only by viewing the motion of the cardiac outline simultaneously. HOLMGREN used a speed of 16 frames per sec, which means an interval of more than 0.06 sec between each frame, and then the most rapid movements cannot be registered in detail, and the curve obtained may be distorted and displaced in time. The appearance of the curve, reproduced in HOLMGREN's paper is such that even a displacement of about 0.06 sec towards diastole would result in an appearance similar to the curves of mitral valve movements now presented.

It is impossible to study rapid movements in detail by methods such as roentgenkymography or single exposures at certain phases of the cardiac cycle and the results thus obtained are therefore of limited significance.

In the three cases of mitral valve calcifications examined, the calcifications were so extensive that the mitral ring was probably also involved, which would mean that the ring moved as the cusps. I intend to study true mitral ring calcifications by the same method in order to determine the movement with accuracy. Animals will also be employed to investigate if normal valves move differently. The heart sounds will then be recorded simultaneously for a closer analysis of the movements in relation to the cardiac phases.

SUMMARY

The pathology, appearance, and frequency of valve calcifications as well as their relation to valvular heart diseases are discussed. The importance of demonstrating the calcification is pointed out and the methods used for localizing calcifications to a certain ostium are described. Cinematography constitutes the most reliable method and has been performed in 6 cases with mitral and/or aortic valve calcifications. A careful analysis has shown that there is a marked difference between the movements of aortic and mitral valve calcifications.

ZUSAMMENFASSUNG

Die Pathologie der Herzklappenverkalkungen, ihre Pathogenese, ihr Aussehen, ihre Beziehung zur Erkrankung der Herzklappen und ihre Häufigkeit ist dargelegt worden. Die Methoden, welche zur Lokalisation von Verkalkungen zu gewissen Ostien benutzt wurden, werden berichtet. Die beste Methode ist die Kinematographie, welche in 6 Fällen mit Mitralis- und/oder Aortaklappenverkalkungen durchgeführt worden ist. Sorgfältige Analyse zeigt, dass ein markanter Unterschied zwischen den Bewegungen der Aortaklappenverkalkung und denjenigen der Mitralisklappenverkalkung vorliegt.

RÉSUMÉ

L'auteur étudie l'anatomie pathologique, la pathogénèse, l'aspect, les rapports avec les cardiopathies valvulaires et la fréquence des calcifications des valvules et il expose les méthodes utilisées pour localiser à un certain orifice les calcifications. La meilleure méthode est la cinématographie, qui a été utilisée dans 6 cas de calcifications valvulaires mitrales et/ou aortiques. Une analyse attentive montre qu'il y a une nette différence entre le mouvement de la calcification de la valvule aortique et celui de la calcification de la valvule mitrale.

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CINEROENTGENOGRAPHY OF THE INTESTINE WITH SPECIAL REFERENCE TO THE EFFECT OF STIMULATING AGENTS UPON MOTILITY

by

S. O. Liljedahl, O. Mattsson and *B. Pernow*

It is a great problem to maintain physiologic conditions during registration of intestinal motility in man and intact animals. CANNON (1902) introduced a roentgenographic technique for such studies, but its employment over long periods in experimental work has naturally been limited by the considerable radiation risks. Investigations of the movements of the human alimentary tract has since then been carried out by numerous workers using widely varying radiographic techniques (see the extensive monographs by COLE 1934, BARCLEY 1936 and GOLDEN 1945). In more recent time MC LAREN, ARDRAN and SUTCLIFFE (1950) studied duodenum and jejunum in man, using an equipment for serial exposure of full size radiographs, 1 to 2 per second.

By the introduction of the image amplifier the problem of cinematographic recording has been facilitated and the risks have been considerably reduced. A fluoroscopic study combined with cinematographic recording of typical motility periods makes documentation of the experimental results possible.

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The image intensifier is already widely used for cineroentgenography (see for instance the extensive reviews by JANKER 1955, PENNING 1955 and MAGNUSSON 1957). As pointed out by PENNING (1955), the method permits of good detailed investigations of the gastro-intestinal tract and valuable information is obtained especially regarding peristalsis and the configuration of the walls of the digestive tract. It has been applied in the diagnosis of among other conditions ulceration and malignancy. Using an image intensifier with a miniature camera and exposing one picture each second CRONE and ARDRAN (1957) studied the effect of morphine sulfate on gastric motility.

The present paper deals with the application of cineroentgenography in studies of intestinal motility in eleven subjects, with special reference to the effect of different smooth muscle stimulating substances, such as prostigmin, and substance P a biologically active polypeptide normally occurring in the intestinal tissue (EULER and GADDUM 1931, PERNOW 1953).

Technique

The patients had fasted for at least five hours before taking the barium meal. After about 3/4 hour the filled jejunum or a proximal loop of the ileum were examined by repeated short fluoroscopic observations, their movements being studied and cineroentgenographic recordings obtained at brief intervals.

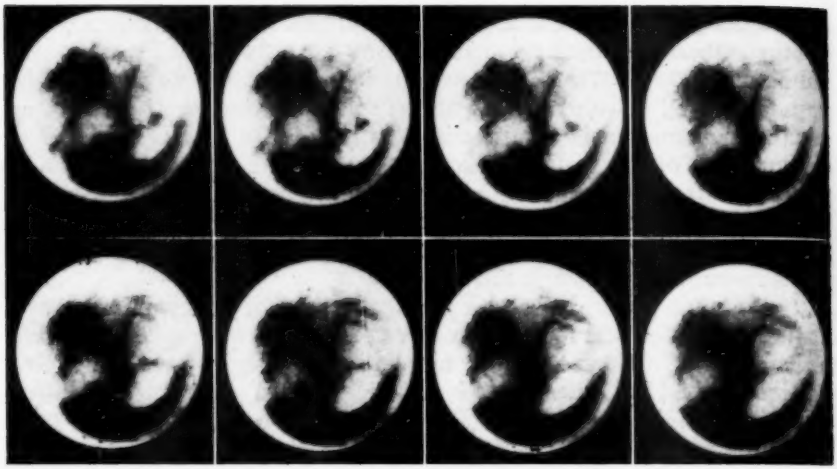
The examinations were performed with the patients recumbent; the fluoroscopy as well as the cineroentgenographic exposures were carried out from below, the image intensifier with the attached cine-camera being located above the patient.

The image intensifier had a field of 5 inches in diameter and a mirror system and viewfinder, fitted to the cine-camera, enabled the simultaneous recording and observation of the field to be obtained. A prism tube was fitted to the viewfinder so that the operator had a choice of vertical and horizontal viewing, the latter usually proving more comfortable with the set-up employed.

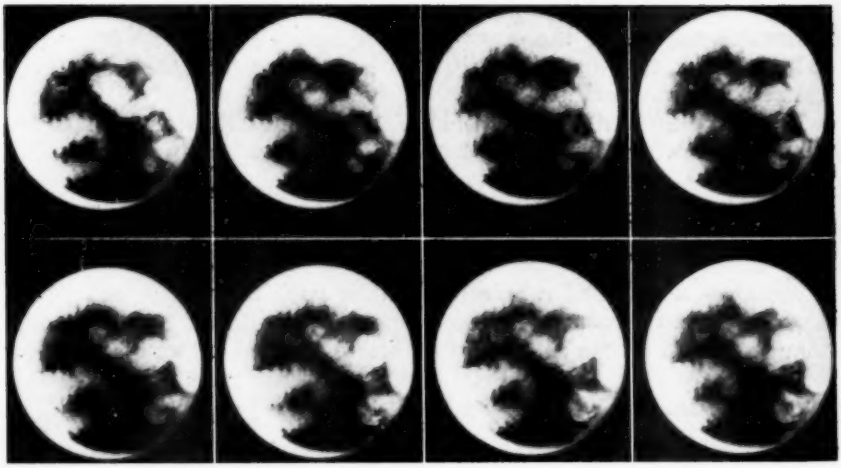
The cine-camera had a rotating shutter with a light sector of 180°. The roentgen apparatus used was capable of kilovoltages up to 200, although limited by the tube and the fluoroscopic table to a maximum of 125; this latter value was therefore employed. The mAs varied between about 5 and 15. The camera speed was 16 frames per second.

Experimental motility studies

The solutions of the substances to be tested were administered by intravenous infusion. Each investigation was started with an infusion of physiologic saline solution for 20 minutes, during which period the initial

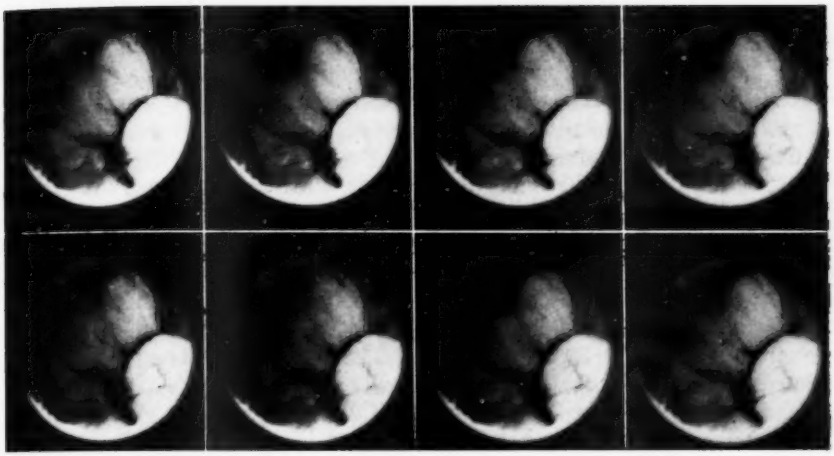


a



b

Fig. 1. Male, aged 30. a) Initial motility during infusion of saline. b) Motility during infusion of substance P (about 40 units/min). Development of peristaltic waves. Both series of frames include movements within a period of 5 seconds.



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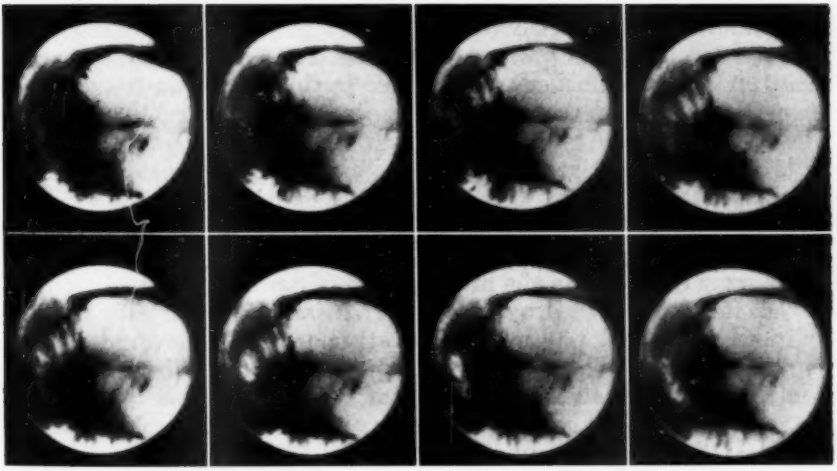

b

Fig. 2. Female, aged 48. Diagnosis: Intestinal paralysis. a) Completely atonic loop of intestine with no movements. b) Same loop of intestine during infusion of substance P (50 units/min). Note development of typical peristaltic wave. All pictures in each series taken within 5 seconds.

intestinal motility was studied and recorded. An infusion of a solution with the substances was then given. Within 20 minutes, for instance, 600 up to 1,000 units of substance P, or 0.5 mg of prostigmin, were administered. During this period the motility was again recorded at repeated short periods. After the infusion was completed the motility was checked for a further 45 minute-period.

A few experimental results are given in the form of a series of frames from the cine-films (Figs. 1 and 2). The method permits a clear demonstration of local segmental contractions dividing the barium content into smaller portions than the peristaltic waves and effectively forcing the contrast media in an aboral direction. The velocity of these contraction waves was estimated to be about 2 to 4 per minute, extending over a segment about 20 to 30 cm in length. The frequency varied greatly between different subjects.

The sequence of films shown in Fig. 1a represents the intestinal motility during the first observation period immediately before the infusion of substance P. Fig. 1b shows the intestinal motility during the infusion of substance P in the same patient. The development of at least three peristaltic waves, as well as increased segmental contractions are observed. Both series of films include the movements within a period of 5 seconds.

A case of intestinal paralysis is shown in Fig. 2, a and b. The bowel was enormously extended and showed no type of movement during an observation time of an hour (a). Frames from one of the periods which was recorded when the patient was given 1,000 units of substance P during 20 minutes infusion are presented in (b). Eight minutes after the commencement of the infusion a few segmental contractions rapidly changed the shape of the intestine and were followed by adequate peristaltic waves extending over about 10 to 20 cm of the intestine in an aboral direction.

Discussion

The main difficulty in the investigation of normal intestinal motility, and the effect of various drugs, is to find a means of carrying it out under conditions which are physiologically satisfactory. The method used in this study enabled the motility in an intestinal loop to be followed by repeated observations without discomfort to the patient.

The radiation dose conditions during cine-roentgenography has been studied separately (LARSSON and MATTSSON). The image intensifier with cine-camera needs about 25 milliroentgen units for every frame correctly exposed. The speed of the camera and the object thickness then influences the amount of radiation required. The dose can be limited by using as high a kilovoltage as possible, a moderate camera speed, and an addi-

tional filter in front of the roentgen tube (including layers of copper, for instance 0.1 mm). The surface dose per minute in examinations of the type in question does not exceed 20 r. In comparison it may be mentioned that an ordinary lateral view of the lumbar region will produce a skin dose of over 20 r (LARSSON 1956). The field irradiated was moved as the contrast media was followed during the exposure and the total skin dose was consequently distributed. The length of the cinematographic exposure did not ordinarily exceed 2 minutes, made up of a series of consecutive periods of 5 to 15 seconds. The fluoroscopic examination required only a small fraction of the roentgenographic intensity and the total screening time did not exceed a few minutes.

In a paper of this description it is usual to show a series of frames to illustrate the changes. The relatively low speed and frequency of the movements of the bowel make this unnecessary and we have consequently chosen every fourth, sixth, eighth or tenth frame. A run of 5 seconds (80 frames, at 16 frames/second) can thus be demonstrated by using every tenth frame. The illustrations are produced in that way and selected from the material mainly to show the possibilities of the method in studying the influence of certain agents upon intestinal motility. It has been found desirable to make reduced prints on 16 mm film by optical reproduction for the analyses of the movements. This is more suitable for use in the special table-top viewers.

The material shown can necessarily give but a limited impression of the value of cineroentgenography in studies of this kind. We feel, however, that the introduction of this method of studying intestinal motility offers new physiologic, clinical and roentgendiagnostic possibilities. An investigation of intestinal motility and the emptying mechanism of the stomach following operation for ulceration is in progress (LILJEDAHL, MATTSSON, PERNOW and WALLENSTEN), and a study of the swallowing mechanism in operated cases of hypopharyngeal diverticula is also proceeding (DOHLMAN et coll.). Both of these will be published.

SUMMARY

The image intensifier combined with a 35 mm cine-camera has been used in an investigation of the effect of certain drugs upon the motility of the intestine in 11 patients.

ZUSAMMENFASSUNG

Ein mit einer 35 mm Kinokamera kombinierter Bildverstärker ist in einer Untersuchung über die Einwirkung gewisser Drogen auf die Beweglichkeit des Darmes in einer Material von 11 Fällen benutzt worden.

RÉSUMÉ

L'intensificateur d'image associé à une camera de 35 mm a été utilisé pour des recherches sur l'effet de certaines substances sur la motricité intestinale dans une série de 11 cas.

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SPONDYLITIS CAUSED BY SALMONELLA TYPHIMURIUM

by

Rasmus Stenström

Spondylitis in association with typhoid diseases not infrequently causes differential diagnostic difficulties. The aim of this article is to elucidate the roentgen diagnostic problems arising in a case of spondylitis caused by salmonella typhimurium.

Earlier publications usually include no definite salmonella type determination, and many cases have not been roentgenologically examined at all. KRAUSE's (1926) typhoid fever material of 25,000 cases contained 13 cases of spondylitis. The incidence of spondylitis varies in different series between 0.18 and 2.7 per cent (LYON 1941). The typhoid spondylitis literature is fairly abundant (BRUDER 1934, GALLUS 1921, HASELHORST 1927, KRAUSE 1926, LYON 1929, 1941, inter alios). VIKING (1941) stated that although typhoid osteitis is well recognized, this does not seem to be true of osteitis due to paratyphoid. ANCHERSEN (1947) maintained that it is impossible to determine with certainty if spondylitis is a more common complication of typhoid or paratyphoid fever.

The published cases of paratyphoid spondylitis are comparatively rare. ROZANSKY, EHRENFELD, & MATOTH (1948) collected 21 cases from the literature in addition to reporting two cases of their own

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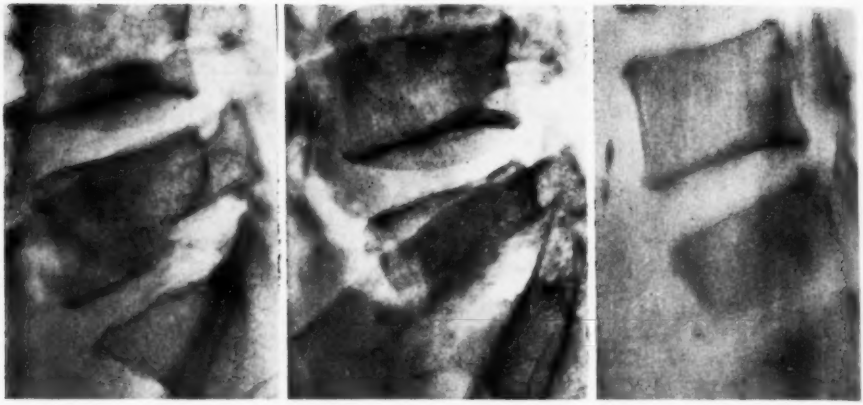


a b c

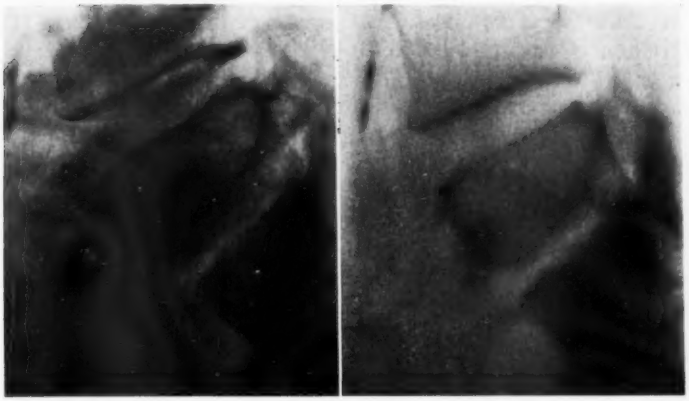
Fig. 1. Salmonella typhimurium spondylitis. a) Fifth week. Joint space normal. Commencing destruction of lower articular surface of vertebra. b) Eighth week. Increased destruction of surfaces of L5 and S1 with reduced joint space. c) Tomography at the same time as in (b).

(ANCHERSEN 1947, KLOSE 1921, PUHL 1930, WAALER 1935, VIKING 1941, inter alios). KRAUSS (1947) published a case of osteomyelitis caused by salmonella typhimurium and referred to two earlier cases from the literature. KRAUSS' own was that of a two-and-a-half year old child with osteomyelitis in the ribs, scapula, pelvis, and femur. I myself have found no cases of spondylitis caused by salmonella typhimurium in the literature.

Report of a case

A. H., lumberman, aged 39 years, had been vaccinated in 1942 against typhoid fever. A prolonged febrile condition developed and proved to be paratyphoid fever caused by salmonella typhimurium. One month after the onset, he complained of stiffness and pain in the lumbar spine and numbness in the legs; pain sensibility on the anterior aspect of the thighs was reduced.

Roentgen examination showed spondylitic changes in the second to fifth lumbar vertebrae. The height of the intervertebral disk between L5 and S1 was normal, but the lower margin of L5 was blurred and showed evidence of early erosion (Fig. 1 a). Two weeks later the joint space had diminished, and destruction of the articular surfaces was apparent; the contours were indistinct of the bones and the calcium content was reduced (Fig. 1, b and c); these observations were interpreted as signs of acute spondylitis. After another month, roentgen examination revealed that the vertebral margins were sharper and the calcium content had increased. Later examinations showed continued regression with bony fusion of the posterior parts of the vertebrae, *i. e.* an incipient block formation (Fig. 2).



a b

Fig. 2. Same case as in fig. 1. a) Conventional examination, $1^1/_4$ years after commencement of disease. Repair with sclerosis and marginal osteophytes. Partial bony ankylosis and reduction in height of disk and body of vertebra. b) Tomography.

Etiology and pathology

According to the investigations of FRAENKEL (1903) living bacilli are found in the bone marrow in cases of typhoid fever during the period from the first to the sixth week of the disease. FRAENKEL was of the opinion that the primary manifestation is a small area of bone marrow osteomyelitis which usually regresses without giving rise to manifest spondylitis; the bacilli, however, may remain dormant in the bone marrow even for decades. Clinical manifestations on the other hand sometimes develop. KLOSE (1921) believed that the bacteria invaded the bone marrow in emboli form via intraosseous vessels and formed an infarct; trauma and congenital or acquired anomalies might be contributory factors. It would seem reasonable to assume that conditions analogous with those in typhoid fever exist in salmonella typhimurium infections.

Roentgen diagnosis

In chronic spondylitis the relation between the primary disease and the spinal condition is frequently difficult to demonstrate. There is usually an interval of months or years between the two pathologic pictures, and only a detailed case history reveals the connection. The

situation may be of some assistance. According to BRUDER (1934) the lumbar region is involved in 56.3 per cent of cases, the thoraco-lumbar junction in 13.6 per cent, the thoracic vertebrae in 12.6 per cent, the lumbosacral junction in 10.7 per cent, the cervical vertebrae in 3.9 per cent and the sacral vertebrae in 2.9 per cent of cases. L3 is the vertebra most frequently involved.

The majority of cases of typhoid and paratyphoid spondylitis reported in the literature were examined roentgenologically in a late stage, and it has generally been a matter of chronic spondylitis with a long interval between the primary disease and the spondylitis. The case presented here was one of paratyphoid spondylitis in which a roentgen examination was performed during the acute stage. The case presents the same characteristics as other acute cases of spondylitis.

I was unable to find any cases in the literature of typhoid or paratyphoid spondylitis with the same fulminant, early, destructive phase and rapid restitution. The case reported presented signs during the peak of the disease. The three relatively acute cases reported in the literature of typhoid spondylitis (GALLUS 1921 and HASELHORST 1927) and paratyphoid spondylitis (PUHL 1930) all started during convalescence, two or three months after the onset of the primary disease.

In the present case the first roentgen examination was carried out one week after the onset of spinal symptoms. The disk height was still normal at that time, and the only change noted was erosion of the lower articular surface of the body of the upper vertebra. Three weeks later destruction was present in both the main articular surfaces, together with decalcification and reduced joint space. This agrees most nearly with LYON's (1941) report that roentgenologic changes in infective spondylitis are observed most distinctly after two to four weeks. According to LYON a process of repair occurs early with a rapid tendency to restitution.

SCHMORL (1929) was of the opinion that the disk is seldom affected in infectious spondylitis. GALLUS (1921), LYON (1929) and PUHL (1930), have demonstrated, however, that the disk usually becomes narrowed even if the lesion appears to originate in the bone marrow. The reduction in the joint space in the roentgenogram may conceivably be due to the disk having been pressed into the spongiosa. LERICHE & JUNG (1931) demonstrated experimentally that the diminution of the joint space can be made to disappear following anesthesia. SCHMORL & JUNGHANNS (1951) concluded that 'thorough anatomic investigations, especially concerning the penetration by the infection of the generally relatively strongly resistant cartilage plate, are unfortunately not yet available.'

The process of repair in the present case coincided with the decrease in fever. Four weeks later, at the third roentgen control, normal calcium

content was observed and ten weeks later, sclerosis. The sclerosis caused eburnation of the spongiosa adjacent to the upper and lower surfaces of the vertebral body. The latest follow-up examination one-and-a-half years after the onset of the disease suggested bony fusion of the vertebrae posteriorly.

The differential diagnosis between acute osteomyelitis, spondylitis of other etiology, and tuberculosis, presented no difficulty in the present case. During an acute infection caused by salmonella typhimurium, spondylitis with a rapid and benign course followed by healing could be followed roentgenologically. Salmonella typhimurium was found in the urine and stools during the whole of the acute stage, and the patient presented a clinical picture of sepsis. It may therefore be reasonably assumed that the spondylitis was caused by salmonella typhimurium.

It is interesting to note that the paratyphoid spondylitis occurred at the peak of the disease, while in those earlier published cases which were roentgenologically examined, the onset was during convalescence. The indications are that salmonella typhimurium predisposes to this fulminant course.

SUMMARY

A case of acute spondylitis in association with *Salmonellosis typhimurium* is described.

ZUSAMMENFASSUNG

Ein Fall von akuter Spondylitis bei gleichzeitigem Vorkommen von *Salmonellosis typhimurium* wird beschrieben.

RÉSUMÉ

Présentation d'un cas de spondylite aigüe associée à une *Salmonellose typhimurium*.

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AUS DEM INSTITUT FÜR KLINISCHE UND EXPERIMENTELLE CHIRURGIE,
PRAG-KRČ, TSCHECHOSLOWAKEI

DIE INDIREKTE LYMPHOGRAPHIE MIT ZEITWEILIGEM VERSCHLUSS DER BLUTKAPILLAREN

von

P. Málek und *J. Kolc*

Die Frage der Darstellung des lymphatischen Systems mittels Kontrastmittel bei Kranken mit Defekten des lymphatischen Systems, ob nun anatomischen oder funktionellen Charakters, ist immer noch im Entwicklungsstadium. Auf Grund überzeugender Arbeiten von KINMONTH u. Mitarbeiter (1953 bis 1955), wird von deren Methode in der Klinik immer mehr Gebrauch gemacht. Es ist ohne Zweifel, dass KINMONTH's Methode eine sehr gute Kontrastdarstellung der Lymphgefässe ermöglicht. Sie hat aber manche Mängel. Es ist dies das rasche Durchdringen des Kontrastmittels durch die Lymphgefässwand, dass in der letzten Zeit von TJERNBERG (1956) betont wurde, und seine rasche Absorption aus den Knoten und aus der Umgebung der Lymphgefässe durch die Blutkapillaren. Ein weiterer Mangel ist aber auch die Tatsache, dass die direkte Lymphographie nur in bestimmten Körperregionen angewendet werden kann. Aus diesen Gründen besteht die ständige Bemühung eine Methode der indirekten Lymphographie auszuarbeiten, die auch in der Klinik anwendbar wäre.

Die Ausarbeitung dieser indirekten Lymphographie stösst aber auf noch grössere Schwierigkeiten. Die für die Klinik geeigneten Kontrastmittel sind einerseits lösbare Stoffe kristalloiden Charakters, andererseits

Bei der Redaktion am 6. Dezember 1957 eingegangen.

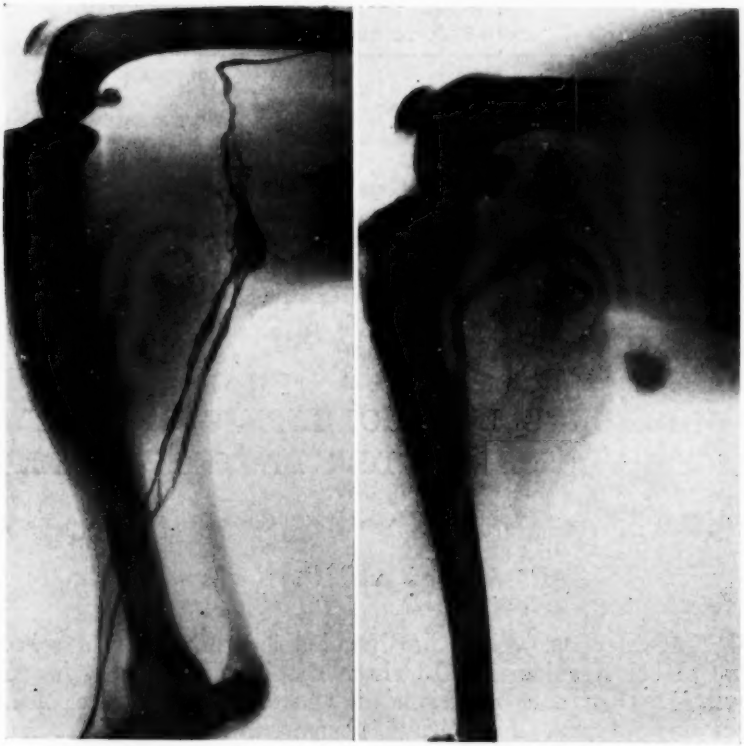


Abb. 1. Indirekte Lymphographie der hinteren Extremität eines Hundes nach Thorotrastapplikation: a) in den Pfotenball, der ein dichtes Lymphkapillarnetz hat, und b) in die Subkutis, die verhältnismässig arm an Lymphkapillaren ist.

sind es Oelstoffe. Keiner dieser Typen ist für die indirekte Lymphographie geeignet, der erste wegen seiner raschen Resorption aus der Stelle der Verabreichung durch die Blutkapillaren, der zweite wegen seiner sehr langsamen Resorption durch das lymphatische System. Deshalb ist es nicht verwunderlich, dass es COLLETTE nur in einem von 50 Fällen gelungen ist durch subkutan verabreichtes Umbradil ein Lymphogramm zu erzielen, und dieses nur angedeutet. Auch GERGELY u. Mitarb. gelang es mit 70 % Joduron in das weiche Gewebe des Beines verabreicht, nicht die Lymphgefässe darzustellen. Nicht einmal Thorotrast, der ideale Stoff für die indirekte Lymphographie bei Tieren, stellt die Lymphgefässe beim Menschen gut dar (ARNULF u. Mitarb. 1954, MARTORELL 1955).

Aus diesen Mängeln geht die logische Forderung hervor, ein neues

Kontrastmittel zu erzeugen, dass für die indirekte Lymphographie in der Klinik genau so geeignet wäre, wie das Thorotrast im Tierexperiment. Da aber dieser Stoff zur Zeit noch nicht existiert, stellten wir uns die Aufgabe, eine Methode auszuarbeiten, die man mit geläufigen Kontrastmitteln ausführen könnte. Drei Hauptbedingungen müssen erfüllt werden:

1. Die Wahl einer richtigen Injektionsstelle mit einem genügend dichten Lymphkapillarnetz;

2. Ein genügender Druck an der Injektionsstelle;

3. Eine verlangsamte Resorption des Stoffes durch die Blutkapillaren, und zwar aus der Injektionsstelle, sowie auch aus der Umgebung der Lymphgefässe und Knoten.

Die erste Bedingung wird von COLLETTE (1955) betont, der meint, dass der Hauptgrund des Misserfolges der erschwerten Bildung des lymphographischen Bildes in der Klinik eben darin besteht, dass diese Bedingung nicht erfüllt wird. Den direkten Beweis dafür erbrachten wir mit unserer folgenden experimentellen Beobachtung. Wenn wir in den Pfotenball eines Hundes Thorotrast injizierten, d. i. einen Kontraststoff, der für die indirekte Lymphographie am geeignetsten ist, bildet sich zwar verschieden schnell, aber immer ein gut interpretierbares Lymphogramm (Abb. 1 a). Ähnlich ist es bei der Applikation in die Haut, von der bekannt ist, dass sie ein reiches Lymphnetz besitzt (SCHDANOW 1952), und wo auch die abführenden Gefässe gut dargestellt werden. Nach der Injizierung des Kontrastmittels in die Subkutis aber, die verhältnismässig arm an Lymphkapillaren ist, bildet sich ein viel weniger deutliches Lymphogramm, das auch weniger konstant ist (Abb. 1 b). Wenn also Thorotrast solche Unterschiede verursacht, können wir sie umso eher bei den geläufigen Kontrastmitteln erwarten.

Was die zweite Bedingung betrifft müssen wir betonen, dass das »frühe« Lymphogramm (die Darstellung der Gefässe und der Knoten) das Resultat des passiven Druckes des Kontrastmittels in die abführenden Lymphgefässe ist, während sich die eigentliche Resorption bei der Bildung des »späten« Lymphogrammes (die Darstellung der Knoten ohne Gefässe) geltend macht, und dies nur bei der Verwendung kolloider oder öliger Kontrastmittel.

An der Injektionsstelle kommt es durch Resorption zu einem schnellen Schwinden des Kontrastmittels, während gleichzeitig der Druck fällt, der nötig ist, um das Mittel in die Lymphgefässe zu treiben. Deshalb dringt das Kontrastmittel in die Lymphgefässe nur in ungenügenden Mengen ein, sodass sich kein guter Kontrast bildet. Gleichzeitig verringert sich die von Beginn an niedrige Konzentration im abführenden lymphatischen System rasch durch die Diffusion in das umgebende Gewebe

a

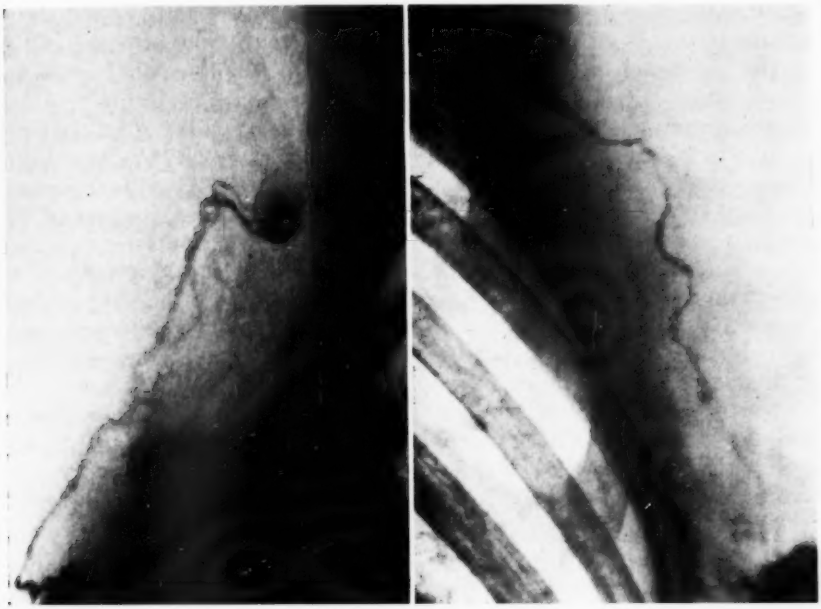
b

Abb. 2. Indirekte Lymphographie: a) der hinteren Extremität eines Hundes (3 Ml Joduron und 0.02 Ml Adrenalin per 1 Ml Kontrastmittel) 30 Minuten nach der Applikation. Injizierung ohne Massage. Beispiel eines gut dargestellten und nicht flüchtigen Lymphogrammes. b) Injizierung an der Milchdrüse einer Hündin. Gut dargestellte abführende Lymphgefässe und regionäre Knoten.

und durch die Resorption durch die Blutkapillaren. Das ist unserer Meinung nach einer der Hauptgründe, warum das lymphographische Bild bei der Lymphographie mit kristalloiden Stoffen so unkonstant und flüchtig ist (BARBERA und PATTI 1956; DURANTEAU u. Mitarb. 1955, COLLETTE 1955).

Wenn es gelingen würde diese Resorption irgendwie zu verlangsamen, könnten bessere Bedingungen für das Durchdringen des Kontrastmittels in die Lymphgefässe geschaffen werden und auch sein schnelles Schwinden aus dem lymphatischen System verhindert werden.

Adrenalin in kleinen Konzentrationen verlangsamt die Resorption



a b

Abb. 3. Indirekte Lymphographien (Triopac, Adrenalin und Massage). a) Eine 43-jährige kranke Frau. Axilla mit Ca der Brustdrüse im oberen inneren Quadrant. Lymphgefässe normal, Knoten von normaler Grösse, Form und Struktur. b) Eine 45-jährige kranke Frau mit Brustdrüsenkrebs und Metastasen in den Axillarknoten. Das abführende Lymphgefäss ist stellenweise erweitert und geschweift, mit einer fast gänzlichen Blockade an der Stelle des von Tumorzellen infiltrierten Lymphknotens.

aus der Injektionsstelle, und das Kontrastmittel bleibt längerer Zeit in dem lymphatischen System.

Bei der Erfüllung der dritten Bedingung für die Bildung des lymphographischen Bildes, handelt es sich also unserer Meinung nach im Prinzip um ein zeitweiliges Verschliessen der Blutkapillaren und deshalb prägen wir für diese Methode der Lymphographie den Namen »indirekte Lymphographie mit zeitweiligem Verschluss der Blutkapillaren«.

Durch die Erfüllung der drei angeführten Bedingungen entsteht ein lymphographisches Bild, das gute Kontrastdarstellungen aufweist und nicht flüchtig ist, und das manchmal sogar annähernd an Lymphogramme erinnert, die mit Thorotrast ausgeführt wurden. Wir wollen zuerst einige Beispiele aus dem experimentellen Material anführen.

Die Abb. 2 a zeigt das indirekte Lymphogramm der hinteren Extre-

mität eines Hundes 30 Minuten nach der Injektion. Dieses Lymphogramm ist ein Beispiel für das Andauern des lymphographischen Bildes.

Die Abb. 2 b stellt das lymphatische System der Milchdrüse einer Hündin dar. Die abführenden Lymphgefässe, sowie auch die regionalen Lymphknoten sind gut sichtbar. Das Vordringen des Kontrastmittels kann man bis in die höheren Abschnitte des lymphatischen Systems verfolgen, bis in den paraaortalen Knoten, der ebenfalls gut dargestellt ist.

Nach diesen äusserst günstigen Erfahrungen im Experiment übertrugen wir die Methode in die Klinik, wo wir sie zur Zeit an Kranken anwenden, die an Brustkrebs leiden. Wir gehen folgendermassen vor: Der narkotisierten Patientin injizieren wir knapp vor dem chirurgischen Eingriff 10 Ml Pyelosil mit 0.2 Ml Adrenalin in die Areoralgegend unterhalb der Brusttwarze. Bekanntlich ist diese Gegend reich an Lymphkapillaren, die die Lymphe in die Axillarknoten abführen.

Nachstehend führen wir die Lymphogramme von 2 Kranken an. Bei der einen (einer 43 Jahre alten Frau) handelte es sich um einen krebsartigen Tumor im oberen inneren Quadrant der Mamma. Das Lymphogramm (Abb. 3 a) stellt die abführenden Lymphgefässe und den regionären Axillarknoten von normaler Grösse, Form und Struktur dar. Bei der zweiten Kranken (einer 45 Jahre alten Frau) handelte es sich um einen Tumor im unteren äusseren Quadrant. Auf dem Lymphogramm (Abb. 3 b), sehen wir das stellenweise ein wenig erweiterte und geschweifte abführende Lymphgefäss. Wir können es bis in die Axilla verfolgen, wo es plötzlich fast gänzlich unterbrochen ist. Weiter scheint es zusammen mit einem feinen Netz von Kollateralen ein Hindernis zu umgehen. Bei der Operation wurde an dieser Stelle ein von Tumorzellen befallener Knoten gefunden.

Abschliessend kann gesagt werden, dass sich die Methode der indirekten Lymphographie mit zeitweiligem Verschluss der Blutkapillaren im Experiment sehr gut bewährt hat, und dass die ersten Erfahrungen in der Klinik ihre Anwendbarkeit bei Menschen ebenfalls in Aussicht stellt. Diese Forschungsrichtung erwies sich also als gangbarer, als z. B. der Versuch das Lymphogramm mit der gleichzeitigen Injizierung von Kontrastmittel und Hyaluronidase zu verbessern, wobei in der Klinik überhaupt kein lymphographisches Bild erreicht wurde (GERGELY u. Mitarb. 1956) und im Experiment nur eine geringe und flüchtige Kontrast-Darstellung (BARBERA und PATTI 1956). Die einzige, zur Zeit unvollständig gelöste Frage ist die, ob das längere Andauern des Kontrastmittels an der Injektionsstelle den lokalen Reizeffekt des Kontrastmittels nicht erhöhen wird. Deshalb wenden wir diese Methode zur Zeit nur dort an, wo anschliessend der chirurgische Eingriff das untersuchte Gebiet mitsamt dem Kontrastmittel abhebt. Diese Frage wird weiter untersucht.

Es muss vielleicht noch betont werden, dass sich diese Methode für die anatomische Darstellung eines bestimmten Abschnittes des lymphatischen Systems eignet, dass sie aber auch zur funktionellen Untersuchung des lymphatischen Systems ausgenützt werden kann. Bekanntlich wirkt sich Adrenalin nicht nur auf die Blutkapillaren aus, sondern auch direkt auf die Lymphgefässe, wo es ihre Konstriktion hervorruft (MONTEIRO, RODRIGUES u. Mitarb. 1957). Die Beigabe von Adrenalin zum Kontrastmittel beeinflusst also nicht nur die »Durchlassungsfunktion« sondern auch die »Transportfunktion« des lymphatischen Systems. Es ist jedoch interessant, dass wir weder im Experiment noch in der Klinik grundsätzliche Unterschiede in der Grösse des Lumens oder der Menge der Lymphgefässe beobachteten, gleichgültig ob die Lymphogramme mit Thorotrast oder mit unserer Methode ausgeführt wurden.

SUMMARY

A method of indirect lymphography with current water-soluble contrast medium has been evolved, the essential feature being a temporary occlusion of the blood capillaries by means of pharmaka. The results under experimental conditions have been encouraging and persistent lymphograms of good contrast were obtained. The first clinical applications of the method have indicated its value.

ZUSAMMENFASSUNG

Eine Methode der indirekten Lymphographie mit geläufigen lösbaren Kontrastpräparaten wurde ausgearbeitet, die hauptsächlich darin besteht, dass ein zeitweiliger Verschluss der Blutkapillaren mittels Pharmaka erreicht wird und die im Experiment ein konstantes, kontrast-dargestelltes und nicht flüchtiges Lymphogramm ermöglicht hat. Die ersten klinischen Erfahrungen deuten auf die Anwendbarkeit dieser Methode hin.

RÉSUMÉ

Les auteurs ont mis au point une méthode de lymphographie indirecte utilisant des produits de contraste solubles courants, dont le principe consiste à provoquer au moyen d'agents pharmacodynamiques une occlusion temporaire des capillaires sanguins; elle a permis d'obtenir expérimentalement une lymphographie contrastée constante et non passagère. Les premiers essais cliniques montrent que cette méthode est utilisable.

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RADIATION HAZARDS ATTENDING USE OF TRANSPORTABLE IMAGE INTENSIFIER

by

Jörgen Kockum, *Kurt Lidén* and *Olof Norman*

The construction of Philip's image intensifier, Müller BV 20, which is mounted on a frame together with a roentgen tube DA 20 is such that it can be placed in surgical, medical, or other departments and used by an operator in the absence of a radiologist (DIETHELM, JÖTTEN, LENTZ and VÖLKEL 1956). The operation factors for the unit range from 0.3 to 3 mA and from 55 to 75 kV, indicating that the radiation exposure rate is comparable to that in conventional fluoroscopy for the higher kV and mA settings. Routine use of the intensifier might thus result in an increase instead of an otherwise possible decrease in the radiation hazards to patients as well as to hospital personnel engaged in roentgenology (OOSTERKAMP 1954, FEDDEMA 1954, BEZOLD, FEINDT and PRESSLER 1956, LACKNER and VÖLKEL 1957).

Since the the manufacturer's instructions contain only scanty and discrepant data on the radiation hazards to personnel handling this type of intensifier, the present investigation was started with the purpose of assessing the risks of excessive radiation exposure of staff and the precautions that should be taken to avoid them.

A preliminary report was presented before the Swedish Society of Radiology on 8 December 1956. Submitted for publication 15 January 1958.

Material and Methods

Determinations were made of: 1) exposure rate in the primary beam, 2) scattered radiation with cylindric water phantoms of 3 different sizes in 2 different positions in the primary beam and 3) radiation leakage from the tube housing.

The exposure rate and the HVL of the primary beam were determined in air with calibrated thimble chambers connected to a Philip's dosemeter. These determinations were made at 55, 65 and 75 kV. The roentgen tube is provided with a permanent filter of 1.5 mm Al.

An investigation was made of secondary radiation from 3 different phantoms of perspex tubes, filled with water with the dimensions 5 × 42 cm, 13.5 × 37 cm, and 22 × 54 cm, which corresponded to the lower arm, the knee-joint, and the thigh, respectively. For comparison, measurements were also made of the secondary radiation from a leg of a calf. The doses were measured with ionisation chambers of condenser chamber type for 200 and 10 mr and adapted for use with Philip's dosemeter. Since the 200 mr chamber is about the size of a fountain pen, 1.2 × 10 cm, and the 10 mr chamber measures 5 × 6.5 cm, the measurements obtained do not represent a point; a certain integration and equalisation occurs over the air volume corresponding to the volume of the chamber, but this is a rule desirable in order to avoid strong specific local variation in the irradiated field. Calibration of these measuring chambers at different qualities of the rays showed a certain energy dependence, which was most marked for the 200 mr chambers. Since no assessments were made of the qualities of the secondary radiation, this energy dependence might sometimes decrease the accuracy of the results of the measurements by about 10 to 20 per cent.

All three cylindrical phantoms were studied in 2 positions; in one the phantom was placed with its nearest part 5 cm from the opening of the small cone, in the other at the same distance from the intensifier. The phantom was always placed somewhat asymmetrically, as is apparent from the schematic illustrations in Fig. 1, which also show the positions of the measuring points. These points were selected to represent the positions of the hands of the examiner. The measuring points in the immediate vicinity of the apparatus were selected to represent the conventional position of the examiner and representative regions of the latter, such as the head, thorax, genitalia, and knees (close to the roentgen tube).

In order to determine any difference between secondary radiation from the water phantom and from the human body with its skeleton, dose measurements were made in one case of the secondary radiation from a fresh leg (calf) with an average thickness of about 12 cm.

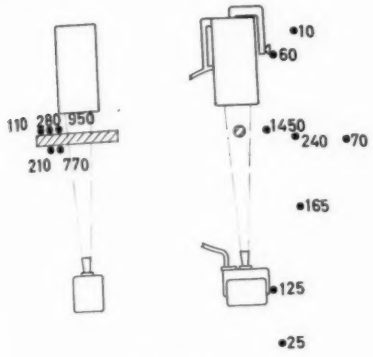

Fig. 1 a

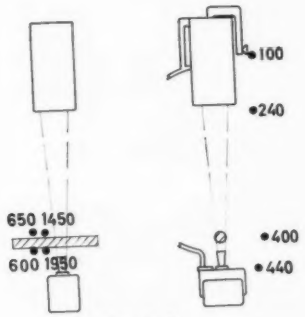

Fig. 1 d

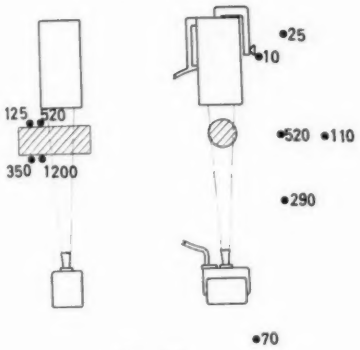

Fig. 1 b

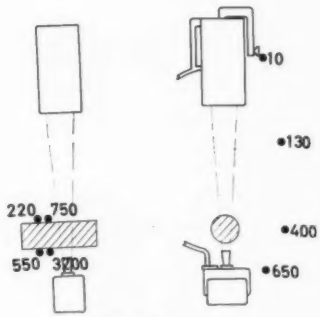

Fig. 1 e

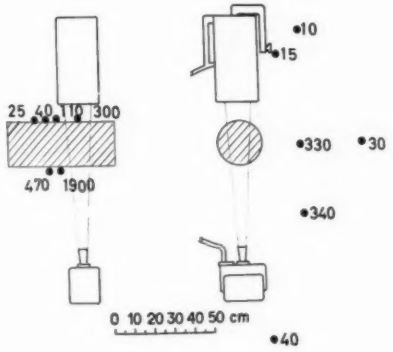

Fig. 1 c

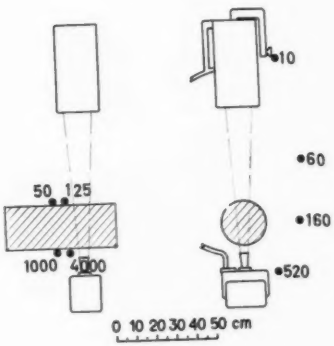

Fig. 1 f

Fig. 1. Sites of measurements of the secondary radiation in mr/hour at 75 kV and 3 mA.

The unavoidable variation in the voltage of the mains resulted in considerable variation in roentgen intensity. Continual checking of the main voltage to the apparatus with the controls on the switch board during the long exposures would have resulted in unwarranted radiation exposure: therefore, when necessary, the current was supplied via a constant voltage transformer and the voltage was controlled by a voltmeter. The tube housing of the roentgen tube was cooled with a current of air from a fan. In these experiments the intensifier was disconnected. Leakage of radiation from the tube housing, and the alignment and collimation of the beam were investigated primarily by photographic methods. Roentgen films were placed round the entire shell and also at the frame of the diaphragm.

Results

The measurements of the primary beam are given in Fig. 2 where the dose rates are shown for distances corresponding to the two standard diaphragms and to different positions of an object.

For these air measurements the inverse square law is almost satisfied. The HVL of the rays in aluminium was found to be 2.0, 1.8, and 1.5 mm, at 75, 65, and 55 kV, respectively. The primary surface dose received by an object will be 10 to 20 per cent greater because of the amount contributed by backscatter. If, for example, an examiner works with the fingers unprotected in the primary beam at the 3 points given in Fig. 1 and at 75 kV and 1 mA his hands will receive about 5 r, 1.4 r, and 0.4 r, within 1 minute. At 55 kV and 1 mA the corresponding figures will be 1.8 r, 0.6 r, and 0.15 r. These settings are for the minimum illumination, which is practical without dark adaption. If the examinations are carried out at 3 mA, the doses received will of course be three times as much.

According to the Recommendations of the International Commission on Radiologic Protection, ICRP, the maximum permissible dose to the hands of those who are occupationally exposed to radiation is 1.5 rad per week. Common sense, of course, dictates that the examiner should never place his unprotected hands in the primary beam. If such exposure cannot be avoided during clinical use of the apparatus, lead-rubber gloves must be worn.

In addition, from a point of view of roentgen technique and in order to minimize radiation hazards, the patient should be as far as possible from the roentgen tube, *i. e.* as close as possible to the intensifier during the examination, which is, however, not always in agreement with recommendations given in the literature for the use of this unit.

The measurements of scattered radiation, which were made in air

around the water phantoms, are summarized in Fig. 1, in which the measuring points are shown drawn to scale. The accuracy of the values given were as a rule not better than ± 10 %, this inaccuracy being due partly to the above-mentioned energy dependence in the range of radiation qualities used.

The dose values found at the measuring points on the actual phantoms are the mean values of measurements at corresponding points on either side of the beam. From the data in Fig. 1 it is seen that the secondary radiation just outside the primary beam on the inside of the object was at most a few per cent of the primary beam; this implies that movement of the examiner's hands only a few centimetres from the edge of the primary beam decreases the risks of radiation considerably. It also shows that the secondary radiation at these measuring points on all phantoms decreased to 50 % from the position near the tube to the position near the intensifier. On the tube side in the latter position, however, it increased with increasing diameter of the phantom from 770 mr/hour for the 5 cm cylinder to 1,900 mr/hour for the 22 cm cylinder. The increase was, however, possibly less than expected and implies that the risks of secondary radiation are not negligible, not even from objects only 5 cm in diameter. The values for the upper position of the 5 cm phantom were somewhat surprising because the upper points in Fig. 1b to the left show higher values than the lower. This might, however, be due in part to backscatter from the intensifier and perhaps also to the fact that the measurements were made with the 10 cm long 200 mr chambers which were placed perpendicular to the cylinder. The chambers thus received radiation from a region somewhat too large in relation to the phantom. However, the measurements are considered to represent fairly well the radiation to which the examiner's hand is exposed in practice.

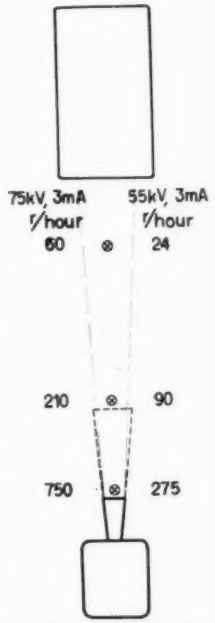

Fig. 2. Measurements of the primary beam.

The results also show that movement of the hand a further 5 cm peripherally markedly reduces irradiation (in the upper position from one third to one fourth of the value some centimetres outside the margins of the beam).

Valuable information on radiologic work with this apparatus, namely the maximum permissible working time for hands, can be calculated from the data given to the left in all the separate sections of Fig. 1. During the examination of an object 13.5 cm in diameter in the upper

position, for example, with the unit operating at 75 kV and 1 mA, an unprotected hand on the tube side of the object will receive 0.4 r/hour if held a few centimetres from the margins of the beam. In other words under such conditions the maximum permissible number of working hours per week would be 3.7. With the tube current set at 3 mA the maximum permissible exposure time would drop to 1.2 hours. If one can manage with 55 kV, the maximum number of working hours according to data not published here will be 2 to 3 times greater. This shows how important it is to use as low a tube current as possible, 1 mA or less for fluoroscopy.

Measurements of the secondary radiations at 75 kV and 3 mA in the vicinity of the apparatus are summarized to the right in all the separate sections of Fig. 1. As to the upper position, it should be observed how the radiation doses of 240, 520, and 330 mr per hour at a point, located 25 cm from the outmost side of the different phantoms, reach the maximum for the intermediate cylinder which in this case is of the same diameter as the cross-section of the beam. In experiments with the largest phantoms, self-absorption of the scattered radiation was observed. In the lower position, which is not suitable in practice, the dose measured was 400 mr/hour for both the 5 and 13.5 cm tubes, but only 160 mr/hour for the 22 cm tube. An additional number of similar conclusions might also be drawn.

For radiologic workers, the ICRP recommendations call for a maximum permissible total body exposure of 300 mr per week. The use of 75 kV and 1 mA resulted in a scattered radiation reading of 100 to 150 mr/hour on the 13.5 cm phantom. This would permit 2 to 3 hour's work per week. At 3 mA only 0.7 to 1 hour exposure time per operator per week would be permissible. This implies that if the number of working hours per week is to exceed the figures given above, the examiner must wear a lead-rubber apron; this precaution is of course desirable in any case.

The radiation at the eyepiece of the intensifier was found to be surprisingly small. Here, however, the agreement between the values was less consistent. Those found for the 5 cm phantom were much higher in both positions than those found for the others. No explanation can be offered for this difference. On the other hand, the doses measured at the level of the knee close to the tube shell were unexpectedly high. Roentgenographic inspection of the tube housing revealed some radiation leakage, which in some directions contributed considerably to the observed doses. Precautions against radiation from the tube housing of transportable apparatus of this type presumably satisfy the requirements of the ICRP. The special type of work under consideration has, however, not been taken into account by the ICRP and complementary regulations on this point are absolutely necessary.

For the softer rays at 55 kV measurements (not included here) showed that the secondary radiation reached values of one half to one third of the corresponding values at 75 kV. In addition the results obtained in a similar study with part of a fresh leg of a calf did not differ significantly from those obtained with a water phantom of the same dimension.

Discussion

In the light of the above observations the recommendations of the ICRP regarding personnel engaged in roentgenologic work are probably not stringent enough, if this type of apparatus is to be widely needed by surgeons, physicians, and others. For non-roentgenologic workers the ICRP is at present considering a suggestion of recommending, for example, a maximum P. T. B. E. of 30 mr per week. This will require special precautions and a carefully designed examination technique with intensifiers if such apparatus are to be recommended for use by persons other than roentgenologic experts. Apart from such rigorous requirements, it is particularly important for a surgeon, for example, not to expose the hands unduly to radiation and thereby run the risk of injury.

The above-mentioned demonstration of radiation leakage from the tube increases the risk for personnel working near it as is the case with the type of apparatus described. Leakage from the holder frame of the diaphragm can also contribute to the dose received by the gonads of patients, especially since the apparatus is intended particularly for the examination of the pelvic regions. The risk of damage during transport of the apparatus is not minimal. This might in turn result in a disturbance of the alignment so that the primary beam might by-pass the intensifier; routine daily inspection of this alignment must therefore be recommended. The risks described above do not fall within the scope of the recommendations of the ICRP for conventional roentgen apparatus. As pointed out, more rigorous requirements must be placed on such transportable apparatus and this in turn requires complementary instructions from the ICRP.

Conclusions

Work with an image intensifier requires the same precautions as work with conventional fluoroscopes. As long as ordinary precautions are observed, *i. e.* the wearing of lead-rubber aprons and gloves, the control of exposure time, and the avoidance of exposure to the primary beam, the radiation hazards to the operator are acceptably small and full advantage may be taken of this technical advance.

SUMMARY

The radiation hazards attending the use of a transportable roentgen diagnostic unit including an image intensifier have been investigated by means of cylindric water phantoms and ionization chambers. The results show that roentgen units of this type, especially if placed in the hands of unskilled workers, require additional radiation safety standards.

ZUSAMMENFASSUNG

Das Strahlungsrisiko bei Verwendung eines transportablen Röntgenapparates mit Bildverstärker ist mit Hilfe von Ionisationskammern untersucht worden, wobei cylindrische Wasserphantome den Patienten ersetzten. Die Untersuchung hat gezeigt, dass für derartige Röntgenapparate teilweise neue Strahlensicherheitsregeln erforderlich sind.

RÉSUMÉ

Les auteurs ont étudié au moyen fantômes d'eau cylindriques et de chambres d'ionisation les dangers d'irradiation que comporte l'emploi d'un appareil de radiodiagnostic portatif équipé d'un amplificateur de brillance. Les résultats montrent que les appareils radiologiques de ce type, en particulier quand ils sont confiés à un personnel inéxpérimenté nécessitent des mesures de protection complémentaires contre les radiations.

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A SCINTILLATION DOSEMETER FOR 31 MeV BETATRON RADIATION

by

Thormod Henriksen

In recent years a scintillation technique has become available in roentgen- and γ-ray dosimetry (BELCHER, and CARR & HINE). The present work deals with special problems which arise in connection with the high energy radiation from a betatron with a peak energy of 31 MeV.

The scintillation dosemeter is similar in construction to an ordinary scintillation counter and consists mainly of three parts: a) the scintillation crystal, b) the light guide and c) the photomultiplier tube.

The scintillation crystal. Doses obtained with a scintillation dosemeter are usually compared with those from ordinary ionization chambers. For such a comparison to be of any value, the relation between the energy absorbed in the air volume of an ionization chamber and the energy absorbed in a scintillation crystal must be a constant and independent of the radiation quality. A crystal having this property is usually called air-equivalent.

The air-equivalence has been treated by BELCHER, and by CARR & HINE, but the methods in question are not satisfactory for high energy radiation, where the range of the secondary electrons is greater than the size of the crystal.

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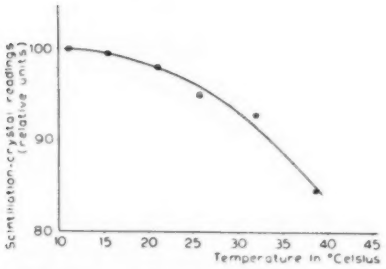

Diagram 1. The efficiency of the anthracene scintillation crystal as a function of temperature.

For high energy radiation the following method is introduced to find air-equivalent scintillation crystals. To every compound or mixture (air, scintillation crystals etc.) may for special purposes an effective atomic number $\bar{Z}$ be ascribed (HENRIKSEN & BAARLI). The requirement for air-equivalence must then be:

$$\bar{Z}_{air} = \bar{Z}_{crystal}$$

The effective atomic number is defined as

$$\bar{Z} = (\Sigma a_i Z_i^x)^{1/x}$$

Z_i is the atomic number for the different atoms which make the compound, and a_i is the fraction of the total electron number which belongs to atoms with atomic number Z_i; x is a quantity which states how the physical process considered varies with the atomic number. This means that the effective atomic number for a compound is not a constant, but varies with the physical process.

For Compton scattering, which varies linearly with Z, $x = 1$, whereas for pair production $x = 2$.

High energy radiation from a 31 MeV betatron is absorbed by pair production and Compton scattering, and in this case x will have a value between 1 and 2. Previous experiments have shown that for a crystal in the form of a cylinder 5 mm in diameter and 5 mm high, $x = 1.4$ (HENRIKSEN 1955, and HENRIKSEN & BAARLI, 1957).

This gives $\bar{Z}_{air} = 7.2$.

Air-equivalent crystals usually consist of organic compounds mixed with inorganic materials. Anthracene ($C_{10}H_{14}$) has an effective atomic number $\bar{Z}_{C_{10}H_{14}} = 5.6$. In this work we used an anthracene crystal

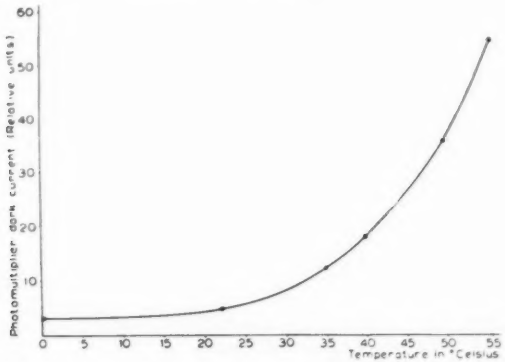

Diagram 2. The dark current of an RCA 931-A photomultiplier tube as a function of the surrounding temperature.

housed in an aluminum cap 0.15 mm thick. When the crystal together with its aluminum cap is considered as one unit an effective atomic number $\bar{Z}_{\text{crystal}} = 7.7$ is obtained and we have nearly air-equivalence for the high energy region (an aluminium cap 0.10 mm thick might give better approach to air-equivalence, but we failed to machine it as thin as that). The aluminum cap acts also as a reflector which offers 20 % more light to the photomultiplier tube.

High energy betatron radiation induces (γ,n) reactions and anthracene contains carbon with a threshold energy of 18.7 MeV for the reaction:

$$C^{12} + \gamma \rightarrow C^{11} + n$$

C^{11} being radioactive with a half-life of about 20 minutes. Radioactivity is therefore induced in the scintillation crystal, this producing a higher and varying background, although it will not contribute to the dose to any appreciable extent.

The light yield of the scintillation crystal depends upon the temperature, which may be determined by placing the crystal in water baths; the results are shown in Diagram 1.

The light-guide. The photomultiplier tube can not be placed directly into the radiation beam, but must be connected to the crystal with a light-guide. Light-guides usually consist of perspex or similar plastic materials suitable for radiation below 1 MeV.

High energy radiation, however, gives rise to high-speed secondary electrons which produce Cerenkov radiation in perspex. During measure-

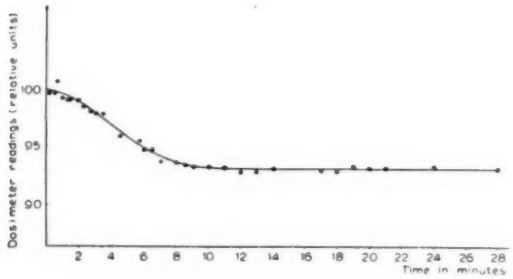

Diagram 3. The fatigue effect in the photomultiplier tube as a function of the time from the start of irradiation with a dose rate of 45 r/min.

ments, the scintillation crystal and some part of the light-guide will be placed in the beam while the rest of the light-guide is out of the beam. That part of the light-guide which is in the beam will vary from one measurement to another, and consequently also the Cerenkov radiation produced in the light-guide.

In our work three different light-guides have been tested: 1) perspex, 2) a high-polished aluminum tube and 3) a glasstube vacuum coated with an aluminum mirror. The light transmitted in these light-guides is in the relation 4.5 : 1 : 1.5. Due to the Cerenkov radiation, perspex had to be discarded and the glasstube has been adopted.

The photomultiplier tube. An RCA 931A photomultiplier tube has been employed. The dark current, which is a part of the background, varies with the temperature, as shown in Diagram 2. Fatigue effect in the photomultiplier tube is observed when the dosemeter is used in connection with radiation of high intensity. The effect is a function of the intensity, and Diagram 3 shows the fatigue effect for the dosemeter for 45 r/min (mostly used at the betatron). Dose measurements cannot be made until some 10 minutes have elapsed. Small intervals of from 1 to 5 minutes without radiation do not introduce fatigue problems after stability has been obtained.

The dosemeter described has been used in connection with the determination of depth dose curves in water and bone for 31 MeV betatron radiation (Henriksen 1955). An ordinary ionization chamber has been used as a monitor and the relation between monitor and dosemeter has been found good.

SUMMARY

A scintillation dosemeter, employing an anthracene crystal and an RCA 931-A photomultiplier and used in connection with dose measurements of the radiation from a 31 MeV betatron is described.

ZUSAMMENFASSUNG

Ein Scintillationsdosimeter wird beschrieben, in welchem ein Anthrazenkristall und ein RCA 931-A Photomultiplikator eingebaut ist; er wird bei Dosismessungen der Strahlung von einen 31 MeV Betatron benutzt.

RÉSUMÉ

Description d'un dosimètre à scintillation à cristal d'anthracène et photomultiplicateur RCA 931-A, utilisé pour les mesures de dose de la radiation d'un bétatron de 31 MeV.

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STUDIES ON THE PENETRATION OF RADIOACTIVE IONS THROUGH HUMAN CERVICAL MUCUS

by

Erik Odeblad and *Björn Westin*

The penetration of diffusable substances such as sodium ions through an aqueous medium follows in principle the Fick diffusion equation:

$$(dm/dt) = D \cdot (dp/dx) \cdot A \qquad (1)$$

In this equation dm/dt is the amount of material transported per unit of time. D is the diffusion coefficient, dp/dx is the concentration gradient, and A is the area available for the transport. In cases of aqueous media containing gels or other substances capable of changing the macro- and microstructure of water, an effective diffusion coefficient D_{eff} (usually smaller than D) can formally replace D in eq. (1).

It has been known for several decades that the human cervical mucus undergoes cyclic variations according to the hormonal stimulus acting on the cervical glands. The percentage of dry substance in cervical mucus (Bergman 1950), the rheologic properties (Clift 1945), and the proton magnetic resonance spectrum (Odeblad and Bryhn 1957) all show pronounced variations in the menstrual cycle. The methods of investigation described by these authors reflect to some extent changes in the composition and internal structure of the cervical mucus. It may there-

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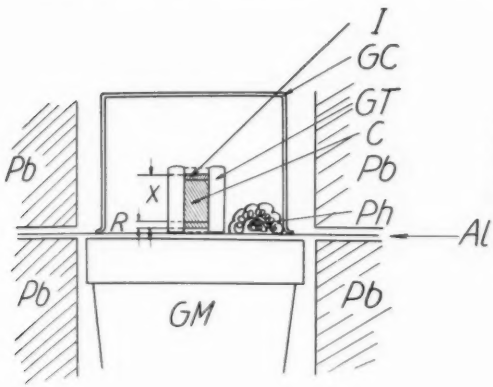

Fig. 1. Experimental arrangement for studying the diffusion of radioactive ions through cervical mucus. *GM* = Geiger Müller tube, *Pb* = lead shields, *Ph* cotton with physiologic saline solution, *GC* glass container. *C* = cervical mucus, *I* = droplet with radioisotope. *Al* = thin aluminium foil. *GT* = glass tube. The mathematical notations *R* and *X* are also given.

fore be suspected that the effective diffusion coefficient also changes during the various phases of the menstrual cycle and pregnancy. For this reason we have attempted to study the effective diffusion coefficient for sodium ions using a radioactive isotope as a tracer.

Method

Fifteen to 20 mg of cervical mucus were introduced into a short glass tube of about 2 mm internal diameter, which was placed on a thin aluminium foil (2.4 mg/cm²) above a G. M. tube having a window thickness of about 3 mg/cm². A small amount (about 1 mm³) of physiologic NaCl solution containing a radioactive tracer (0.1 to 0.5 μC) was placed on the upper surface of the mucus (Fig. 1). As the diffusion spreads downwards, the counting rate in the G. M. tube increases when the radioactive ions come within the region of the maximum range, R, of the beta particles. The counting rate was recorded every fifth minute and a diagram showing this rate as a function of the time was obtained (Diagram 1).

Within a certain time interval the situation within the sample may be regarded more or less as a steady state with a nearly constant concentration (p_u) in the upper part of the sample and a nearly linear concentration gradient, $G = dp/dx \approx (p_u - p_l) / (X - 2R/n) \approx p / X$ within the greater part of the sample (Diagram 2). In that case eq. (1) may be written:

$$(dm/dt) = D_{eff} \cdot G \cdot A \qquad (2)$$

p_l is an average concentration in the lower part of the sample, and X is the depth of the sample.

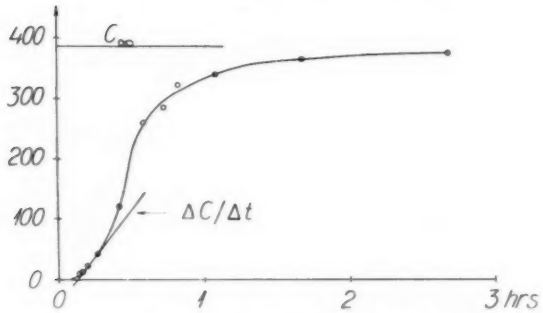

Diagram 1. Typical example of experimental curve.

In that case, as is evident from the diagram, the counting rate is equal to

$$C_i = Q\,A \int_0^R (1 - r/R)^3 \cdot G_1\, r dr = QAG_1R/20 \qquad (3)$$

where G_1 is the average gradient between O and R and $G_1 < G$. Q is the instrumental efficiency factor and $(1 - r/R)^3$ is the binominal formula for transmission of medium energy beta rays (ODEBLAD 1957). If the sample could be turned 180 degrees and counted, the counting rate would then be equal to

$$C_u = Q\,A \int_0^R (1 - r/R)^3 \cdot GX\, dr = QAGX\, R/4 \qquad (4)$$

provided $X \geqslant R$. C_u is determined most practically after following diffusion to final equilibration. The counting rate is then C_∞ and $C_u \approx 2C_\infty$.

The ratio of counting from both sides is accordingly

$$C_i/C_u = (R/5\,X) \cdot (G_1/G) \qquad (5)$$

Going back to eq. (2) we obtain approximately:

$$(RA/n)\ (\triangle C/\triangle t) = D_{eff} \cdot (2C_\infty/X) \cdot A \qquad (6)$$

where (R/n) is the effective depth (ODEBLAD 1957) of the counted volume. Here $(\triangle C/\triangle t)$ is the experimentally obtained increase of counting rate. Since usually $C_i \ll 2C_\infty$, we have approximately

$$D_{eff} = (R/n)\ (\triangle C/\triangle t)\ X/2C_\infty) \qquad (7)$$

$(\triangle C/\triangle t)$ is then measured at the point where $C_i/C_\infty = 2R/5\,X\,(G_1/G)$.

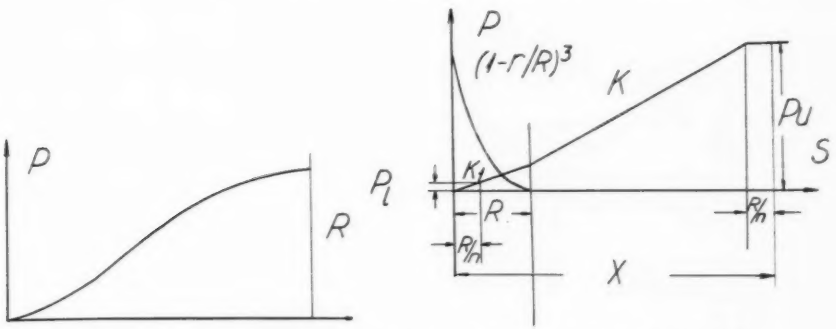

Diagram 2. Real (R) and simplified (S) situation in cervical mucus during diffusion. Ordinate = concentration of isotope in mucus abscissa = distance from G. M. tube. $(1 - r/R)^3$ is the beta ray transmission curve.

X was usually about 0.5 cm. R for certain different isotopes is given in Table 1. The ratio G_1/G is difficult to estimate and influences the experimental value of D_{eff}. However, the error due to G_1/G will be of similar magnitude in all determinations if X and R are of the same magnitude and, if D_{eff} is given in logarithmic form, the error will be constant. It is assumed here that $G_1/G = 1/2$. This value is supported by graphic representations of the concentration in the tube.

Many other serious errors are introduced in D_{eff} through the simplifications made in the preceding discussion. This holds especially for the assumption that the concentration gradient is even far from correct because the gradient may locally be of the double average value. D_{eff} may on this basis be in error by a factor of two or so but, as will be seen below, the D_{eff} will vary by a factor of about ten in the menstrual cycle. In order to indicate that we do not measure the true value of D_{eff} we shall, however, allow the notation D_{exp} to denote our experimental uncorrected value for D_{eff}.

All measurements were undertaken at + 21° C.

Table 1

Substance	Isotope	Half-life	Beta energy MeV	R cm water	R/n cm water	$Dx\ 10^5$ cm² per sec in water	γrays
H^3O	H^3	12 y	0.019	0.0007	0.0001	1.8	No
Na^+	Na^{22}	2.6 y	0.55	0.2	0.06	1.7	Yes
Cl^-	Cl^{36}	4 x10^5 y	0.7	0.3	0.1	1.4	No
SO_4^{--}	S^{35}	87 d	0.17	0.03	0.01	1.0	No
HCO_3^-	C^{14}	5,600 y	0.16	0.025	0.08	1.2	No
Glucose	C^{14}	5,600 y	0.15	0.025	0.08	0.8	No
Br^-	Br^{82}	36 h	0.47	0.17	0.06	1.1	Yes

Results and Discussion

Our experimental results using Na^{22} are collected in Diagram 3. These show D_{exp} in a logarithmic scale related to the phase of menstrual cycle of some apparently healthy women.

In the postmenstrual period the diffusion of ions through the cervical mucus takes place rather rapidly. When midcycle is approached and the cervical secretion becomes transparent and abundant and shows arborization, the diffusion coefficient appears to be considerably suppressed. The rather surprising observation that the diffusion proceeds slowest when the percentage of water is highest, requires some consideration.

Ions in aqueous solutions are hydrated, which means that they orient the water dipoles around themselves with an energy of the order of ee'/r^2, where e is the ionic charge, e' the water dipole moment and r the mutual distance. For the water molecules closest to an ion this energy is of the order of a few eV. Assuming now a process of evaporation and condensation (SHAW and ELSKEN 1955) for controlling the movement of these ions through the adsorbed water of the cervical mucus, the time for such an elementary process is

$$t = (h/kT) \exp (+ E_{vap} /kT) \tag{8}$$

where h is Planck's constant, k is the Boltzmann constant, T is the absolute temperature and E_{vap} the energy of vaporization (of the order of 0.5 eV per molecule). If E_{vap} becomes high for the water in mucus the time t also becomes long and the movement of ions will be slower.

If this consideration is applicable, this study supports the idea that the cervical mucus contains water adsorbed on the mucoid with a higher energy of vaporization than ordinary water. Such an assumption is also in agreement with the rheological properties of cervical mucus and the magnetic resonance data mentioned above (ODEBLAD and BRYHN 1957).

We may also express the diffusion coefficient in terms of the viscosity of the cervical mucus by the well-known equation

$$D = (k\,T/12\pi\eta r) \cdot F \tag{9}$$

The low value of D at midcycle indicates high intrinsic viscosity of the midcycle mucus. Here η is the viscosity (in poise), r is the radius of the molecule and F is a dimensionless factor depending on the shape and on the mechanical, electrical, and magnetic multipole moments of molecules; it is of the order of unity. Since the intermolecular contribution to proton magnetic spin-lattice relaxation is given by

$$T_1, \text{ inter} = D \cdot (40\pi/3\gamma^4 h^2 N) \tag{10}$$

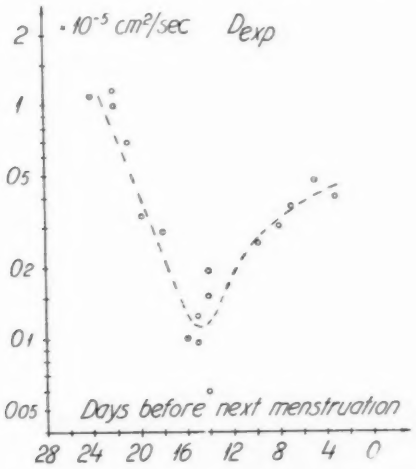

Diagram 3. D_{exp} for various days of regular ovarian cycles.

(see ANDREW 1955, p. 117), the connection between the low diffusion coefficient and a component with short T_1 in midcycle mucus (ODEBLAD 1958) is obvious. (In eq. (10) γ is the magnetogyric ratio of the proton and N is the number of protons per cm³.)

Hydrodynamically the cervical mucus does not behave as an ideal (Newtonian) fluid. It shows many such anomalous properties as 'flow elasticity', 'Spinnfähigkeit'. The determination of the viscosity of cervical mucus is therefore very difficult. The discussion presented above indicates, however, that the determination of the diffusion coefficient will give some information on the intrinsic viscosity of cervical mucus, but that the effects related to the vapor pressure of 'hydrated' water as well as other effects will probably also contribute to the experimental value of the diffusion coefficient.

We would state here that cervical mucus, at least at midcycle, is strongly heterogenous and with probably different effective diffusion coefficients in different regions and directions.

The present approach to the problem is only preliminary. More suitable experimental arrangements and theoretical approaches are being investigated and will be reported later.

It seems possible that the determination of the effective diffusion coefficient could give quantitative information on the cervical response to oestrogenic hormones in clinical use.

SUMMARY

The penetration of Na^{22} ions through human cervical mucus during various phases of the menstrual cycle has been studied. During the 'water phase' of cervical mucus at ovulation, the penetration is considerably hindered. Attempts are made to correlate this finding with some other properties of the mucus.

ZUSAMMENFASSUNG

Die Penetration von Na^{22}-Ionen durch menschlichen Zervixschleim ist während verschiedener Phasen des Menstruationszyklus studiert worden. Während der «Wasserphase» des Zervixschleimes bei der Ovulation war die Penetration sehr langsam. Es wird versucht, diesen Befund mit einigen anderen Eigenschaften des Schleimes zu korrelieren.

RÉSUMÉ

Les auteurs ont étudié la pénétration des ions Na^{22} dans le mucus cervical de la femme au cours de diverses phases de cycle menstruel. Cette pénétration est très diminuée pendant la phase de la glaire filante à l'ovulation. Les auteurs essaient de relier ce fait à certaines autres propriétés du mucus.

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PROTON MAGNETIC RESONANCE OF HUMAN MILK

by

Erik Odeblad and *Björn Westin*

The proton magnetic resonance spectra and proton magnetic spin-lattice relaxation time of human milk at various periods after childbirth have been determined and form the subject of the present communication.

Method

The proton resonance was observed at +20° C in a field of 4,930 gauss at 21 Mc/sec using the spectrometer described by LINDSTRÖM and BHAR (1956), but somewhat modified. The resolution was about 1 to 2 parts in 10^7. Samples of 0.05 to 0.2 cm^3 were used and rotated at a speed of 1,000 to 2,000 rev/min during the recording. A partial or nearly complete separation of milk plasma and cream often occurred during the rotation and this complicated the interpretation of the spectra. In addition, because the milk is an emulsion of approximately spherical fat globules in milk plasma, the bulk diamagnetic field within each fat globule is homogenous (except from magnet inhomogenities) while on the other hand the form factor for the surrounding plasma is complicated and may cause diamagnetic field inhomogenities resulting in a broadening of the plasma peak.

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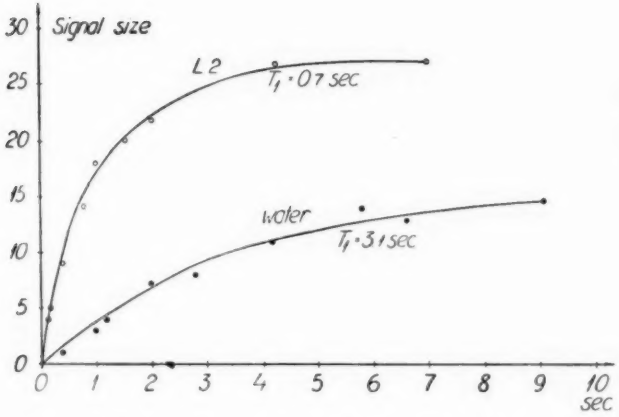

Diagram 1. Growth of proton signals after saturation for a milk plasma (L 2) and water sample.

The spin-lattice relaxation time (T_1) of the milk plasma was measured by observing the growth of the signal after saturation (Diagram 1). T_1 for fat globules was too short to be determined in that way but some information was obtained by the method of progressive saturation in which the plasma and fat peaks are compared in the same record. (For details of the theory and technique see the book by ANDREW 1955.)

Discussion of results

The resonance signal of milk is composed of three components: W, T, and F (Fig. 1). Of these, W is the true plasma peak, T is a 'tail' on the plasma peak, and F is the peak due to the fat. Some characteristic values of peak area, line width, shift, and T_1 are given in Table 1. The higher the fat contents, the higher was the F peak. Diagram 2 shows T_1 for various days after birth. T_1 for the F peak was about 0.03 sec.

The resonance of the plasma peak is composed of two components, W and T, W having a position and line width similar to that of water. The T component, on the other hand, appears to be similar in nature to the broad component identified in human cervical mucus (ODEBLAD and BRYHN 1957) and certain other biologic materials. The fact that the relaxation time of T_1 for milk plasma is shorter than for water is probably related to the viscosity of milk plasma being higher than the viscosity of water. It is, in addition probable that the paramagnetic material may

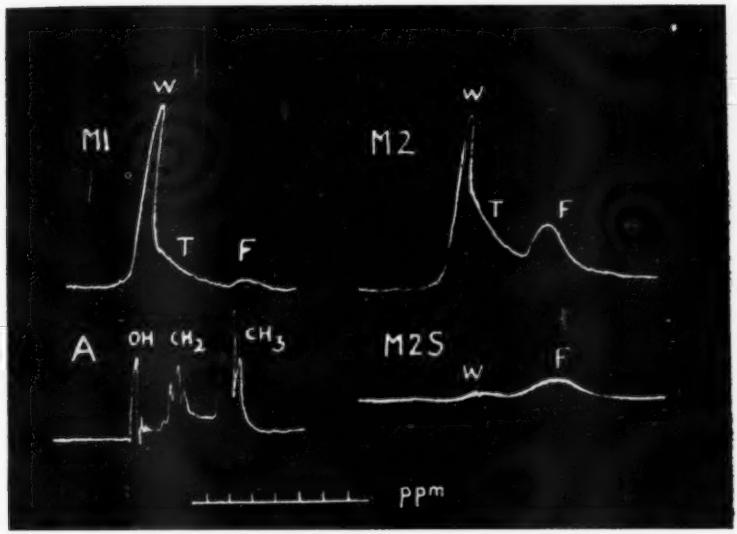

Fig. 1. Proton magnetic resonance signals from milk at sixth day after birth (M 1). M 2 is from the cream formed in the same sample. The three components W, T, and F are clearly distinguishable. M 2 S is sample M 2 recorded during saturation; the W peak is here lower than the F peak. A is an alcohol sample for calibration. Scale in ppm.

Table I

Peak	Relative area	Line width, ppm	Shift, ppm	T_1 sec
W	0.4	0.2	0	1.5
T	0.2	0.8	+0.5	?
F	0.4	0.8	+3.5	0.03

be present in milk plasma. No significant trend in T_1 of milk plasma as a function of the day after birth is apparent.

The position of the F component is very close to that of aliphatic organic compounds with long carbon chains, *e. g.* n-hexane in aqueous suspension has a shift of +3.5 ppm. The short T_1 of this peak is also consistent with the assumption that it arises from protons in the fat molecules. A spin life time of 0.03 sec would give a line width of about 5 cycles. The observed line width is, however, about 20 cycles, so that the spin-spin interaction time T_2 may be of the order of 0.01 sec. The broadening may also be due to unresolved partial peaks within the F structure. The large width and low height of the F peak makes it difficult to use this method for measurement of low fat contents in milk samples.

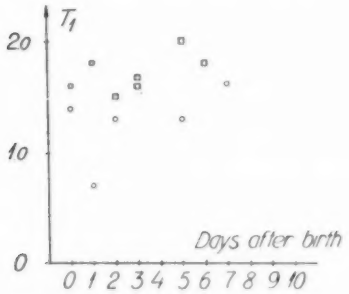

Diagram 2. Proton spin-lattice relaxation, T_1, of milk plasma for various days after birth. Circles stand for primiparas, squares for multiparas.

SUMMARY

Methods for the examination of the proton magnetic resonance spectra of human milk at the various days of the puerperium and measurement of the spin-lattice relaxation time are described. A peak in the spectrum of shift 0 ppm (water reference) was identified as the milk plasma. It was associated with a broad (1 ppm) peak of low intensity, shifted about +0.5 ppm. At +3.5 ppm there was a peak arising from the milk fat. The spin-lattice relaxation time was about 1.5 sec for plasma and of the order of 0.03 sec for the milk fat.

ZUSAMMENFASSUNG

Das magnetische Protonresonanzspektrum menschlicher Milch verschiedener Tage des Puerperiums wurde untersucht und die Spin-Gitter-Relaxationszeit gemessen. Ein Maximum im Spektrum 0 ppm (Wasserreferenz) konnte dem Milchplasma zugeordnet werden. Es war mit einem breitem (1 ppm) Maximum geringer Intensität verbunden, welches etwa +0.5 ppm verschoben war. Bei +3.5 ppm fand sich ein dem Milchfett zuzugehöriges Maximum, dessen Breite ca 1 ppm war. Die Spin-Gitter-Relaxationszeit war etwa 1.5 Sek. für das Plasma und in der Grössenordnung von 0.03 Sek. für das Milchfett.

RÉSUMÉ

Les spectres de résonance magnétique des protons dans le lait humain des différents jours de «puerperium» ont été examinés et le temps de relaxation spin-réseau a été mesuré. Une résonance dans le spectre de déplacement 0 ppm (par rapport à l'eau) a été identifiée comme la résonance de plasma du lait. Elle était associée à une large (1 ppm) résonance de faible intensité, déplacée à environ + 0.5 ppm. À +3.5 ppm il y avait une résonance dûe aux matières grasses du lait, dont la largeur était environ 1 ppm. Le temps de relaxation spin-milieu était environ 1.5 sec pour le plasma et de l'ordre de 0.03 sec pour les matières grasses du lait.

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INTESTINAL WEIGHT LOSS IN MICE IRRADIATED BY ROENTGEN RAYS, GAMMA RAYS, AND FAST NEUTRONS

by

M. A. Patetta-Queirolo, M. L. Randolph and *J. A. Sproul, Jr.*

Mice die earlier after median lethal doses of neutrons than after comparable doses of roentgen rays or gamma rays (UPTON et coll. 1956; CLARK et coll. 1957), the maximal death rates being observed at approximately 5, 9, and 11 days after exposure to neutrons, roentgen rays, and gamma rays, respectively. From the work of QUASTLER et coll. (1951) and BOND et coll. (1954), indicating the relation between the time of death in the early postirradiation period and changes in the gastrointestinal mucosa, it has been postulated by many observers that the early mortality of neutron-irradiated mice reflects a high relative biological effectiveness (RBE) of neutrons for intestinal injury. This has also been suggested by the more frequent occurrence of intestinal tumors in mice exposed to neutrons than in those exposed to roentgen rays and gamma rays (NOWELL et coll. 1956).

This study was undertaken for a determination of the RBE of 250 kV peak roentgen rays, Co^{60} gamma rays, and 14.1 MeV neutrons for causing

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injury of the small intestine of the mouse, the biological effects being related to the linear energy transfer (LET) of the radiation as proposed by ZIRKLE (1952, 1954). In the assessment of radiation damage, intestinal weight loss was used as the criterion, since CONARD (1953, 1954) and STORER et coll. (1957) showed that the degree of weight loss of the small intestine of the rat is linearly related to the dose of roentgen rays and of gamma rays.

Methods

A total of 400 ten-week-old female RF mice weighing 20 to 30 g were randomly selected for irradiation. Each group consisted of ten animals, which were caged together throughout the experiment, receiving Purina Chow and drinking water *ad libitum*. Animal quarters were maintained at constant temperature (78° F) and relative humidity (50 %).

Roentgen irradiation. The animals were irradiated in a circular lucite cage with twelve separate exposure compartments. The cage was rotated on a turntable at 7 rpm to insure uniform irradiation (UPTON et coll. 1956). Animal ventilation was adequate and no anoxia was observed. A G.E. Maxitron 250 kV peak roentgen machine, operated at 250 kV, 0.62 mA, TSD 70 cm, with 3 mm of Al external filtration and inherent filtration equivalent to 0.1 mm of Al (HVL 0.44 mm of Cu) was used to deliver the radiation. Dose-rate calibrations of the roentgen machine output were made before and after irradiation with a Victoreen 100 r condenser-type ionization chamber inside the circular lucite cage filled with paraffin mouse phantoms. Assuming that the value for W (the number of electron volts required to produce an ion pair in air) is 34, GRAY found that 1 r unit of roentgen rays and gamma rays deposits 96 ergs/g in soft tissue or that 1 r unit = 0.96 rad (GRAY 1956). This factor was used to convert all measured air doses to tissue doses. The dose rate was 3.6 to 3.7 rad/min, with dose over the range of 46 to 650 rad.

Co^{60} gamma irradiation. The Co^{60} gamma-ray source has been described by KIRBY-SMITH and DANIELS (1953). Dose-rate measurements were based on data obtained with a special thimble-type gamma-ray dosemeter used in the calibration of the gamma-ray source (DARDEN et coll. 1951). The animals were arranged along an isodose arc on a semicircular exposure rack (UPTON et coll. 1956) in which the difference between radii from the point source to the individual mouse cages was less than 0.1 cm. Mice were caged in celluloid exposure tubes (1.4 cm exposure-tube radius and 7.0 cm exposure-tube length). These tubes were arranged on the semicircular exposure rack containing ten exposure-tubes. The distance from the axis of the Co^{60} gamma-ray source to the

axis of the individual exposure tubes was 36 ± 0.1 cm. The dose rate was 3.6 to 3.7 rad/min, with doses over the range of 93 to 744 rad.

Fast neutron irradiation. A commercial Cockcroft-Walton 250 kV accelerator with a well-focused beam up to 1 mA, producing monoenergetic fast neutrons of 14.1 MeV energy by the T(d,n)He^4 nuclear reaction was used (RANDOLPH 1956). Mice were irradiated while caged in perforated, celluloid exposure tubes (diameter 2.8 cm and length 8 cm) at a mean distance 12 cm from the target of the accelerator. The range of doses was 126 to 798 rads delivered at 4.8 to 4.9 rad/min. The neutron dosimetry was based on intercomparisons of several methods of neutron dosimetry and two independent monitors were used for each exposure. The dosimetry techniques have been described elsewhere (EDINGTON and RANDOLPH 1958).

Intestinal atrophy. A modification of the technique of CONARD (1953) and STORER et coll. (1957) was used. Twenty-four and 48 hours after exposure, the unirradiated control and the irradiated test animals were killed and their intestinal weights determined. Daily determinations of intestinal weights were made from 0 to 7 days after irradiation. The small intestine from the pyloric juncture to the ileocecal valve was carefully dissected free, its contents flushed out with saline, and the excess saline squeezed out by 'stripping down' the tissue with the fingers. The intestinal wet weight was measured with a Roller-Smith precision torsion balance and the averages for each group of five or more mice were obtained. CONARD (1953) has shown that changes in weights determined by this technique are not accompanied by changes in the ratio of wet weight to dry weight.

Linear energy transfer (LET) values. Of the various possible ways to describe the LET spectra produced by these radiations in wet tissue (BOAG 1954, RANDOLPH 1957, and EDINGTON and RANDOLPH 1958), we have chosen the track average (see Table 2); however, the qualitative description of the variation of intestinal weight loss as a function of LET holds regardless of the LET average chosen.

Results

After either neutron or gamma irradiation, there was rapid weight loss of the small intestine, which reached a maximum by the second day, followed by recovery toward the control range at 3 to 5 days, according to the pattern observed after roentgen irradiation by CONARD (1954). Average weights at 24 and 48 hours after irradiation with gamma rays,

Table 1

Average weights of irradiated intestines at 24 and 48 hours after irradiation

Radiations	Doses (rad)	Average weights (g)	
		24 hrs	48 hrs
Co^{60} gamma rays	0	1.2093	1.2708
	93	1.1562	1.2142
	186	1.1064	1.1484
	372	1.0486	1.2247
	558	0.8771	1.0284
	744	0.8384	0.9836
250 kV peak roentgen rays	0	1.3263	1.3433
	46.5	1.2450	1.3833
	372	1.0811	1.0904
	465	1.0928	1.1603
	651	1.0238	0.9529
14 MeV neutrons	0	1.2564	1.1288
	126.5	1.1289	1.0188
	195.2	0.9363	1.1121
	403	0.9446	0.8211
	798.5	0.8156	0.6281

Table 2

Linear regression coefficients for intestinal weight on dose

Weight measured at	Radiations	Approx. track average LET keV/μ	95 % Confidence intervals	
			Intercept (g)	Slope (g/10^4 rad)
24 hours	Co^{60} gamma rays	0.27 [a]	1.21 ± 0.12	5.19 ± 2.80
	250 kV peak roentgen rays	3.0 [b]	1.31 ± 0.06	4.76 ± 1.73
	14 MeV neutrons	12.0 [c]	1.15 ± 0.08	4.63 ± 1.80
48 hours	Co^{60} gamma rays	0.27	1.26 ± 0.07	3.61 ± 1.65
	250 kV peak roentgen rays	3.0	1.36 ± 0.07	5.83 ± 2.01
	14 MeV neutrons	12.0	1.14 ± 0.07	6.59 ± 1.51

[a] From H. E. JOHNS, 1956.
[b] For 250 kV, HVL 0.4 mm of Cu.
[c] EDINGTON and RANDOLPH, 1958.

Table 3

RBE of radiations for the induction of intestinal weight loss at 24 and 48 hours after irradiation

Weight measured at	Radiations compared	RBE $\pm$ 1 SE for intestinal weight loss	RBE for $LD_{50}/30$ days (from SPROUL and RANDOLPH 1957)
24 hours	Roentgen rays to gamma rays	0.85 ± 0.27	
	Neutrons to gamma rays	0.94 ± 0.31	
	Neutrons to roentgen rays	1.10 ± 0.29	
48 hours	Roentgen rays to gamma rays	1.50 ± 0.43	1.39
	Neutrons to gamma rays	2.02 ± 0.51	1.47
	Neutrons to roentgen rays	1.35 ± 0.28	

roentgen rays, and fast neutrons are shown in Table 1. Linear regressions of weight on dose were fitted by the method of least squares to the six sets of data. The resulting intercepts and slopes are given in Table 2. At the 95 % confidence level only the 24-hour neutron data showed a significant deviation from linearity. The intercepts for the neutron and roentgen irradiated groups differed significantly. Because of this variation in the average initial intestinal weights of various groups, the percentage of initial weight lost per unit dose is probably a better index of radiosensitivity than the weight loss per unit dose or slope given in Table 2. The RBE values given in Table 3 were derived from comparisons of such indices. No two of the 24-hour values differ significantly; however, at 2 days the neutron to gamma-ray RBE is significantly different from unity at the 90 % confidence level. Doses of gamma rays above 768 rads caused no further weight loss at 1 and 2 days, resulting in a plateau effect, such as was noted in mice by CONARD (1954).

Discussion

Our RBE of 1.35 of 14 MeV neutrons compared with roentgen rays for the production of intestinal weight loss at 48 hours is significantly lower than the value of 2.3 obtained for mice irradiated by neutrons from a cyclotron with an energy ranging from 3 to 20 MeV (CARTER et coll. 1956). Differences in LET spectra, or possibly of the dose rate or of the strain, age, and sex of the mice may account for this variation. The RBE value of CARTER et coll. was derived from regressions of the logarithm of weights on dose; however, for radiations with a plateau of maximum weight loss, independent of dose, one might anticipate that the relation may be better expressed as the regression of weight on log dose. Although our data have also been analyzed in the first way, without much change in the RBE values as given in Table 3, we have preferred to present the linear relation rather than an exponential, because of the relative simplicity of the former.

Although there was definite weight loss within 1 day after exposure, there was no significant differentiation at this time between the relative effectiveness of the various types of radiations. On the second day, however, the qualitatively anticipated RBE's were observed, with the effectiveness of neutrons being greatest and that of gamma rays least. If one assumes that photon irradiation near the $LD_{50}/30$ day level induces relatively few intestinal deaths and that neutron irradiation at the same level of acute lethality induces primarily intestinal deaths (UPTON et coll. 1956, CLARK et coll. 1957), and if one presupposes that the loss of intestinal weight is directly proportional to intestinal damage, then the RBE for intestinal weight loss should be greater than for acute lethality,

as noted (CARTER et coll. 1956). However, the RBE for intestinal weight loss was not as much higher as might be expected (Table 3). For example, the ratio between the dose of neutrons and that of gamma rays required to cause intestinal death (*i. e.* death within 6 days after irradiation) is approximately one to four (SPROUL, UPTON, RANDOLPH, unpublished data), suggesting that intestinal weight loss may not be well correlated with the degree of intestinal injury and may not, therefore, fully reflect the severity of damage.

Although under the conditions of this experiment the RBE of the radiations increased with their LET, it should be emphasized that in mammalian systems the RBE is influenced by variables other than the LET of the radiation, *e. g.* on variations in dose rate, depth dose, and inhomogeneities in dose deposition. The latter are of greater significance for large animals than for mice.

Acknowledgements

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SUMMARY

Groups of 10-week-old female RF mice were exposed to graded doses of Co^{60} gamma rays, 250 kV roentgen rays, or 14 MeV fast neutrons. The weight of the small intestine decreased during the first 48 hours after irradiation as a linear function of dose over the range 50 to 700 rads. No significant differences between radiations in the production of this effect were observed 1 day after irradiation, but at 2 days the RBE was found to increase with LET, being 1.0, 1.5, and 2.0 for gamma rays, roentgen rays, and neutrons, respectively. The RBE of neutrons for intestinal weight loss was appreciably higher than for 30-day lethality, in keeping with the hypothesis that the earlier mortality of mice exposed to neutrons, as opposed to roentgen rays, results from relatively greater injury of the gastrointestinal tract by neutrons.

ZUSAMMENFASSUNG

Gruppen von 10 Wochen alten weiblichen RF-Mäusen wurden mit gradierten Dosen von Kobalt 60-Gammastrahlen, 250 kV-Röntgenstrahlen oder 14 MeV-schnellen Neutronen exponiert. Das Gewicht des Dünndarmes nahm während der ersten 48 Stunden nach der Bestrahlung als eine lineäre Funktion der Dosis im Gebiete von 50 bis 700 rad ab. Keine signifikanten Unterschiede zwischen Strahlenarten in Bezug auf das Auftreten dieses Effektes wurden einen Tag nach der Bestrahlung beobachtet, aber nach 2 Tagen fand man, dass die relative biologische Wirksamkeit (RBE) mit dem LET (linear energy

transfer) ansteigt und 1,0, 1,5 und 2,0 für bezw. Gammastrahlen, Röntgenstrahlen oder Neutronen ist. Die RBE der Neutronen bezüglich der Abnahme des Dünndarmgewichtes war bedeutend grösser als für die LD 50/30, welches mit der Hypothese in Übereinsstimmung steht, dass das frühzeitige Absterben der mit Neutronen exponierten Mäuse, im Gegensatz zum Verlauf bei Benutzung von Röntgenstrahlen, auf einer relativ grösseren Schädigung des Magen-Darmkanales durch Neutronen beruht.

RÉSUMÉ

Des groupes de souris RF femelles agées de 10 semaines ont été exposés à des doses étagées de rayons gamma du Co^{60}, de rayons roentgen de 250 kV ou de neutrons rapides de 14 MeV. Le poids de l'intestin grêle diminue pendant les premières 48 heures après l'irradiation suivant une fonction linéaire de la dose dans l'intervalle de 50 à 700 rad. Les auteurs n'ont pas observé entre ces diverses radiations de différence significative sur la production de cet effet un jour après l'irradiation, mais ils ont constaté qu'au bout de 2 jours le RBE augmente avec le LET, étant de 1,0, 1,5, et 2,0 pour les rayons gamma, les rayons roentgen et les neutrons respectivement. Le RBE des neutrons pour la perte de poids intestinale est sensiblement plus grand que pour la léthalité à 30 jours, conformément à l'hypothèse que la mortalité précoce des souris exposées aux neutrons, à la différence des rayons roentgen, résulte d'une atteinte relativement plus grave du tube digestif sous l'effet des neutrons.

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LIVER RESPIRATION IN NORMAL IRRADIATED AND SYNKAVIT-TREATED RATS

Endogenous respiration in phosphate buffer

by

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The experiment was designed to study in vitro the endogenous respiration of rat liver slices from normal animals, irradiated animals, animals treated with various doses of synkavit, and animals pretreated with synkavit and then irradiated. All the measurements were made on a Warburg apparatus.

MITCHELL (7, 8) has reported on various substances which increase the response of higher living organisms to ionizing radiations, with special regard to tumour tissue. One of the best known of these is the tetrasodium salt of 2-methyl-1,4-naphthohydroquinone diphosphate, a synthetic vitamin K known as synkavit. Treatment with this substance before roentgen irradiation is known to increase the mortality of rats, and since it is accumulated by the liver, and the liver istelf is a fairly large, homogeneous organ and therefore amenable to such an investigation, we chose to study the effects on liver metabolism of synkavit alone and combined with roentgen irradiation.

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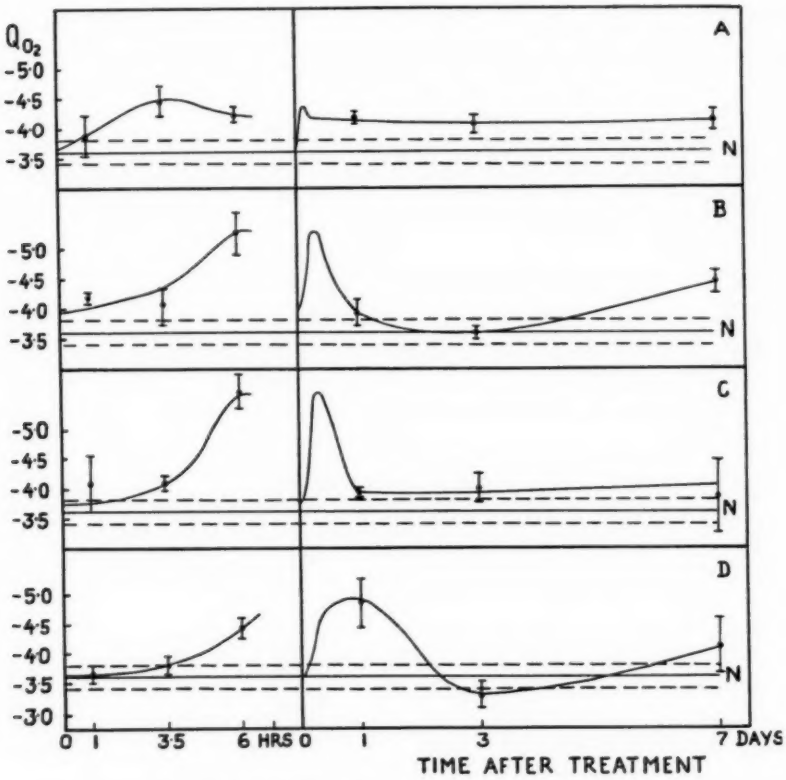

Diagram 1. Variation of Q_{O_2} with time after treatment for groups 5 to 8.

A — irradiated animals.
B—C and D — animals pretreated with 10, 20 and 30 mg synkavit, respectively, and irradiated 20 min later.
N — normals.

Experimental

Male rats of the Wistar strain, 7 to 8 weeks of age, weighing 150 to 180 g were used. They were reared on our standard mouse cake, which has the following composition:

Fish meal 1.2 kg	Lucerne meal 1.2 kg
Ground wheat 10.2 kg	Cod liver oil 0.036 kg
Linseed meal 0.4 kg	Skim milk powder 0.3 kg

Vitamin E oil 0.025 kg (containing 125 mg tocopherol)

Treatment. The rats were divided into eight groups:

1	Untreated controls which were taken at different time intervals during the experimental period
2 to 4	Animals receiving 10, 20 and 30 mg synkavit respectively
5	Irradiated animals
6 to 8	Animals pretreated with 10, 20 and 30 mg synkavit respectively and irradiated 20 minutes later

The injection medium was Synkavit-La Roche, injected intraperitoneally. The radiation treatment was a single dose of 450 r whole body irradiation (0.95 mm Cu HVL, dose rate 40 r/min), the animals being restrained under irradiation in perspex cages. Animals were killed by fracture of the neck and then decapitated to give more or less uniform exsanguination. The livers were removed as quickly as possible and kept in ice-cold, oxygen-saturated, KREBS (3) phosphate buffer (pH 7.1). In groups 2 to 8 animals were killed 1, 3.5, 6 hours, 1, 3 and 7 days after treatment, time zero being taken as the start of the irradiation or 20 minutes after injection.

Respiration measurement technique. The livers were each sliced into sections of 0.4 to 0.5 mm thickness using a MC ILWAIN (6) tissue slicer. In some few cases slicing was done by hand, but this gave no discernible difference in results. Approximately 100 mg of slices were transferred to a 15 ml Warburg flask with 3 ml of the same phosphate buffer as mentioned above. The central well was filled with 0.2 ml of 20 % potassium hydroxide, and the flask flushed with oxygen for 10 minutes, and then fitted onto the Warburg apparatus. After 20 minutes equilibration at 37.5°C, readings of oxygen uptake were started and repeated at 10 minute intervals. Apart from the details mentioned here the technique used with the Warburg apparatus was exactly as described by UMBREIT (11). After the last reading, the slices were filtered off onto a sintered glass filter and dried to constant weight at 105°C. In all determinations the oxygen uptake per milligram dry tissue was found to be proportional to elapsed time within at least the first hour, and the results are expressed as μl O_2 uptake per mg dry tissse per hour, the so-called Q_{O_2}.

Statistics. From two to seven duplicate measurements were made on each liver and the variations between such duplicate determinations was 5 to 15 %. These measurements were averaged for each animal. The number of animals in each experimental group is given in Table 1. In Table 2 is shown the mean value of Q_{O_2} for each group and the error of this mean, calculated as

$$\text{error} = \sqrt{\frac{S^2}{n}}$$

where S^2 is the estimate of the variance, and n the number of animals in the group. In comparing two treatments or any treatment with the controls, the usual 'Student' test was applied where there seemed any possible likelihood of significance.

Table 1

Number of animals in each experimental group

Treatment	Time after treatment					
	1 hour	3.5 hours	6 hours	1 day	3 days	7 days
10 mg synkavit	5	3	3	3	3	3
20 mg synkavit	3	3	3	3	3	3
30 mg synkavit	3	3	3	3	3	3
450 r	5	5	5	5	5	5
10 mg synkavit + 450 r	3	3	3	3	3	3
20 mg synkavit + 450 r	3	3	3	3	3	3
30 mg synkavit + 450 r	3	4	3	3	3	3
Control	10					

Discussion of results

It seems from our results that synkavit alone has some effect on the oxygen uptake of the liver, but this does not show any systematic variation with time or dosage. The effect of radiation alone is a significant increase in respiration from 6 hours to 2 days after treatment. The aninals receiving both synkavit and irradiation showed the same effect, though somewhat earlier, 4 hours to 1 day, and for the highest dose of synkavit, 30 mg, the change was irreversible, at least over the period which we studied, 7 days.

The literature contains reports on the effect of roentgen irradiation of liver cells under a variety of conditions. KAHLSTORF (2), using a glucose substrate in a similar experiment to ours, reports on an irreversible decrease in Q_{o_2} from —10.98 to —10.53 measured on a rather small number of animals. MAASS (5) found no change in respiration after a dose of 20,000 r given in vitro. Reports by RAJEWSKI (10) and PAULY and RAJEWSKI (9) show that doses over 100,000 r given to liver tissue cultures result in depression of respiration. KUNKEL (4) and his colleagues used doses from 200 to 1,400 r whole body irradiation and studied endogenous respiration of liver homogenates; under these conditions they found an elevation of oxygen uptake.

Our results would seem to be in reasonable agreement with the nearest comparable report on radiation effects, that of KUNKEL, and to support the findings of MITCHELL on the sensitizing effect of synkavit to irradia-

Table 2

Mean value and error of mean of Q_{O_2} for each experimental group

Treatment	Time after treatment					
	1 hour	3.5 hours	6 hours	1 day	3 days	7 days
10 mg synkavit	−3.17±0.29	−3.24±0.42	−3.73±0.44	−2.68±0.31	−3.70±0.22	−3.35±0.36
20 mg synkavit	−5.00±0.34	−4.35±0.17	−3.45±0.42	−3.59±0.79	−3.29±0.17	−4.52±0.29
30 mg synkavit	−4.09±0.24	−3.50±0.35	−3.32±0.25	−2.35±0.32	−3.03±0.04	−4.79±0.40
450 r	−3.65±0.17	−3.81±0.15	−4.43±0.16	−4.84±0.41	−3.30±0.22	−4.11±0.46
10 mg synkavit + 450 r	−4.07±0.47	−4.09±0.13	−5.62±0.28	−3.93±0.02	−3.99±0.25	−3.86±0.60
20 mg synkavit + 450 r	−4.17±0.10	−4.04±0.31	−5.25±0.36	−3.93±0.22	−3.58±0.09	−4.43±0.18
30 mg synkavit + 450 r	−3.88±0.34	−4.45±0.25	−4.23±0.13	−4.17±0.10	−4.06±0.14	−4.12±0.18
Controls	−3.61±0.21					

tion. They also give an interesting parallel to our earlier findings (1) that the same dose gives an increase in the liver sterol synthesis in vitro during the first day after irradiation.

Histology. As shown in our earlier investigation (1) only slight morphological changes were found in a few cells of the liver after 7 days after irradiation.

Acknowledgement

The authors would like to express their gratitude to Professor J. Nielsen for his unfailing support and interest.

SUMMARY

Whole body roentgen irradiation of rats with 450 r is shown to increase the endogenous respiration of liver slices. Pretreatment with synkavit results in a similar but earlier effect, which becomes irreversible after larger doses.

ZUSAMMENFASSUNG

Eine Totalröntgenbestrahlung von Ratten mit 450 r steigert die endogene Respiration in Leberscheiben. Vorbehandlung mit Synkavit hat eine ähnliche, jedoch frühzeitiger auftretende Wirkung, welche nach grossen Dosen irreversibel wurde.

RÉSUMÉ

Les auteurs montrent que l'irradiation roentgen de tour le corps par 450 r augmente chez les rats la respiration endogène de tranches de foie. Un traitement préalable par le synkavit est suivi du même effet, mais plus précoce, qui devient irréversible après de plus fortes doses.

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BOOK REVIEWS

CHANGES IN LIVER CELL ELEMENTS DURING STIMULATED PROTEIN SYNTHESIS. A CYTOCHEMICAL STUDY. By G. F. Bahr. 111 pages, 59 illustrations, 4 tables. Acta radiol. Suppl. 147 (1957). Sw. Kr. 25: —.

Actively synthesizing cells in rat liver were studied: 1) after starving and refeeding; 2) after hepatectomy and 3) after feeding the cancerogenous p-dimethylaminoazobenzene by means of the following methods: scanning interference microphotometry of isolated liver nuclei, a modified histochemical reaction for protein-bound sulfhydryl groups in combination with scanning microspectrography, and a new method for the determination of dry weight using the electron microscope.

With the interferometric technique 1,700 nuclei prepared from frozen-dried material were studied and the results of the measurements recorded in 25 histograms representing the size, weight and concentration of nuclear material in populations of nuclei. Increase in size and mass at constant concentration was observed after starving. After refeeding, decrease in mass and size resulted in increased concentration. A tendency to normalization was obvious after twelve hours refeeding. Hepatectomy effected an initial increase in concentration of a similar magnitude as for refed animals, which was followed by a decrease in concentration caused by an increase in size and a certain loss of nuclear material. Feeding of the cancerogeneous substance caused a decrease in concentration of the nuclear material, and the mass was slightly increased. For DAB treated livers there was an increase in nuclear size.

Starving, hepatectomy and azo-dye treatment increased the SH-content of the liver sections by about 30 per cent as compared to normal material. The onset of rapid protein synthesis decreased the excess of protein-bound sulfhydryl content of the liver to about 20 per cent below normal. The variations in sulfhydryl content were mainly a consequence of similar changes in the protein content as disclosed in the biochemical determinations but in the DAB treated material a net increase in protein-bound sulfhydryl is seen, while a relative decrease is found after refeeding and on the second day after hepatectomy.

The microsome fraction exhibited quantitative changes in protein content — ribonucleic acid as a rule corresponding to values indicated in the literature. The weight of the average ribonucleoprotein particle is estimated with the electron microscope to be $(6.75) \cdot 10^{-19}$ g. It is assumed to represent mono-macromolecules. No significant deviations from this value have been found to arise with variable experimental conditions, and it is tentatively suggested that ribonucleoprotein occurs principally in this form independent of the total amount of RNA per cell. From the results of sulfhydryl titrations and the increase in mass due to specific electron staining of the particles, the amount of sulfhydryl has been estimated as being the approximative equivalent of 250 glutathione molecules.

Autoreview.

ET KLINISK OG EXPERIMENTELT ARBEJDE OVER HOFTEALLOPLASTIK SOM BEHANDLING OVERFOR EGNEDE TILFAELDE AF FRACTURA COLLI FEMORIS OG SPECIELT FØLGETILSTANDE HEREFTER (Alloplasty of the hip as treatment in suitable cases of fracture of the neck of the femur and in sequels of such fracture. Summary and conclusions in English). By R. Movin. 275 pages, 90 figures. Ejnar Munksgaard, Copenhagen 1957. D. Kr. 25:—.

The main theme of this book is that it should be possible to improve the therapeutic results in fracture of the femoral neck and its sequelae by greater individualization of the methods of treatment. Earlier clinical experience with arthroplasty of the hip has not been favorable. Some of the reasons for this are, in Movin's opinion, faulty positioning as well as incorrect design and structure of the prostheses. He has therefore designed new prosthetic appliances which are placed more vertically than the original Judet prostheses. His views as to the positioning are undoubtedly correct, but in an investigation of this type they should have been based on a study of the mechanical loads to which the hip joint is subjected; for it is the load direction that should determine the shape and position of the appliance.

The book contains nothing of major interest to the roentgenologist. Much of it is founded on a roentgenologic analysis, and very careful measurements of the lever arm of the gluteus medius muscle are presented. Yet there is no reference to the manner in which these measurements were made, to the roentgen projections on which they were based, or to how these projections were obtained. A further shortcoming is the complete absence of lateral projections.

The principal merit of Movin's work is that it affords clinical verification of those conclusions regarding the position of the prosthesis, which have earlier been drawn from theoretical studies of the loads on the hip joint.

The book is in Danish but includes a relatively comprehensive summary in English.

Stig Backman.

ADVANCES IN RADIOBIOLOGY. Proc. 5th Intern. Conference on Radiobiology, held in Stockholm 15th—19th August 1956. Edited by George Hevesy, Arne Forssberg, and John D. Abbatt. 560 pages, 45 plates. Oliver and Boyd, Edinburgh 1957. 77s. 6d.

This volume contains the papers and discussions from the 5th International Conference on Radiobiology held at Stockholm in 1956 and covers practically all the fields of current research in radiobiology, comprehensively treated by specialists in each.

Several methods of modifying the effects of irradiation are now recognized and include the injection of chemical substances before the irradiation is received or by therapeutic measures following its administration. Spectacular progress has been made in the transfer of living bone marrow cells to lethally irradiated animals. The possibility that cells from foreign species may substitute radiation-destroyed cells was discussed from cytologic and immunologic points of view. The mechanism of the protective effect afforded by certain sulphhydryl compounds, such as cysteamine, has been much clarified in recent years. Interesting results in this field were also presented at the meeting.

A chapter is devoted to investigations on the accumulation of various radioactive isotopes in the body, methods of evaluating radiation doses, and attempts to release from their sites isotopes which have already been incorporated. Radiation leucaemia as well as irradiation effects on the haemopoietic system are discussed. The latter subject is particularly comprehensive and covers both experimental studies and observations in patients. Data on the clinical employment of alkoxyglycerol treatment are included.

The book also includes chapters on the genetic effects and recent advances in the possibilities of modifying to some extent even this radiation damage while several chapters are devoted to more theoretical matters. The volume thus gives the reader an extensive survey over recent advances in radiobiology and can be warmly recommended to all interested in this field.

Arne Forssberg.